Form PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
9052-111	
U S APPLICATION NO (If known, see 37 CFR 1 5)	
10/088245	
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE
PCT/GB00/03568	18 September 2000
PRIORITY DATE CLAIMED	
17 September 1999	

TITLE OF INVENTION
TARGET FOR ANTIVIRAL THERAPY

APPLICANT(S) FOR DO/EO/US
ANTSON, Alfred; MAITLAND, Norman

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4)
7. ☐ Amendments to the claims of the International Application Under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report Under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☒ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4)
20. ☐ Other items or information:

10/088245

JC13 Rec'd PCT/PTO 15 MAR 2002

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO. PCT/GB00/03568	ATTORNEY DOCKET NO 9052-111

21. ☒ The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492(a) (1) - (5)):	CALCULATIONS	PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO..... **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO..... **$890.00**		
International preliminary examination fee 37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)..... **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)..... **$100.00**		
ENTER APPROPRIATE BASE FEE AMOUNT =	$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	40 - 20 =	20	x **$18.00**	$360.00	
Independent Claims	15 - 3 =	12	x **$84.00**	$924.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$280.00**	$1008.00	
TOTAL OF ABOVE CALCULATIONS =				$	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2			-	$	
SUBTOTAL =				$	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	$	
TOTAL NATIONAL FEE =				$	
Fee for Recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property			+	$	
TOTAL FEES ENCLOSED =				$2240.00	
				Amount to be refunded:	$
				charged:	$18.00

a. ☒ A check in the amount of $2240.00 to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 50-0220 in the amount of $18.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-0220. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Jarett K. Abramson

Date: March 15, 2002

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Susan E. Freedman

Susan E. Freedman

Attorney's Docket No. 9052-111 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Antson et al.	Examiner:	To be assigned
Serial No.:	PCT/GB00/03568	Group Art Unit:	To be assigned
Filed:	September 18, 2000		
For:	Target for Antiviral Therapy		

Date: March 15, 2002

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U.S. Patent and Trademark Office
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Arlington, VA 22202
Attn: DO/EO/US

PRELIMINARY AMENDMENT

Sir:

Prior to the examination of the above application, please amend the above referenced application as follows. Please enter the following amendments prior to the calculation of the filing fee. Pursuant to the rules for amendments under 37 C.F.R. §1.121, the claims have been amended herein using the rewritten claims format. The present amendment also includes a section entitled **"VERSION WITH MARKINGS TO SHOW CHANGES MADE"** attached hereto.

IN THE SPECIFICATION:

Please amend the specification as follows:

On page 1 after the title of the invention please add:

RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 371 from PCT/GB00/03568, (published under PCT Article 21(2) in English), filed on September 18, 2000, which claims priority to Great Britain Application Serial No. 9921938.8, filed on September 17, 1999, the disclosures of which are incorporated by reference herein in their entireties.

IN THE CLAIMS:

Please enter the amended claims as follows:

2. (Amended) The E2NT dimer protein of Claim 1 wherein the residues lie on opposite sides of an N-terminal domain.

3. (Amended) The E2NT dimer protein of Claim 1, wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer.

4. (Amended) The E2NT dimer protein of Claim 3 comprising three clusters.

5. (Amended) The E2NT dimer protein of Claim 3 wherein a first cluster of vital residues is associated with interactions between N1 and N2 domains and comprises any one or more of the following residues: Ile82, Glu90, Trp92, Lys112, Tyrl38, Val145.

6. (Amended) The E2NT dimer protein of Claim 3, wherein a second cluster of residues is associated with N1 interactions and comprises either or both of residues Trp33 and Leu94.

7. (Amended) The E2NT dimer protein of Claim 3, wherein a third cluster of residues is associated with N2 interactions and comprises any one or more of the following residues: Pro106, Lys111, Phel68, Trp134.

8. (Amended) The E2NT dimer protein of Claim 1, further comprising residues associated with transactivation and/or replication properties of E2.

9. (Amended) The E2NT dimer of Claim 8, wherein the residues comprise any one or more of the following residues: Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69.

10. (Amended) A method for determining the structure of a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein, wherein the E2NT dimer protein and any of its mutations are mapped onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and the effect of mutations on folding of the E2 protein.

11. (Amended) The method according to Claim 10 in rationalised antiviral drug design.

12. (Amended) A method for identifying and/or selecting a candidate therapeutic agent, the method comprising:

determining interaction of a E2 N-terminal module (E2NT) dimer in a sample by contacting said sample with said candidate therapeutic agent and measuring DNA loop formation in E2 *in vitro*.

13. (Amended) The method according to Claim 12 further comprising identifying and/or selecting an antiviral candidate therapeutic agent.

14. (Amended) The method according to Claim 13, wherein the identifying and/or selecting of the antiviral candidate therapeutic agent depends on its ability to interfere with or block interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.

15. (Amended) A method of treating an HPV infection in a subject comprising:

introducing an E2NT dimerisation inhibitor in said subject.

16. (Amended) The method according to Claim 15 further comprising treating warts, proliferative skin lesions and/or cervical cancer.

18. (Amended) Use of a dimerisation surface of an crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof according to

Please cancel claim 33 without prejudice or disclaimer.

Please add the following new claims:

34. (New) A method for designing a potential antiviral compound for the prevention or treatment of an HPV infection, comprising:

a) obtaining crystals of the E2NT dimer protein such that the three dimensional structure of the crystallized E2NT dimer protein can be determined to a resolution of about 1.9 Å or better,

b) evaluating the three dimensional structure of the crystallized E2NT dimer protein;

c) synthesizing the potential antiviral compound based on the three-dimensional crystal structure of the crystallized E2NT dimer protein;

d) contacting an HPV virus with the potential antiviral compound; and

e) assaying the HPV virus for infectivity or monitoring the virus for activity, or both, whereby a decrease in the infectivity of the virus or a change in the activity of the virus indicates the compound may be used for the prevention or treatment of an HPV infection.

35. (New) The method according to claim 34, wherein the antiviral compound is a peptide or polypeptide.

36. (New) The method according to claim 34, wherein the E2 N-terminal module dimer protein or homologue thereof comprises residues vital for transcriptional and replication activities of said protein.

37. (New) The method according to claim 36, wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer.

38. (New) The method according to claim 37, wherein said E2NT dimer protein comprises three clusters.

39. (New) A method for designing a candidate compound for screening for binding to or inhibition of an HPV infection, comprising:

a) utilizing the three dimensional structure of a crystallized E2NT module dimer protein wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer; and

b) designing a candidate binding compound based on the three-dimensional crystal structure of the crystallized E2NT dimer protein for binding to said dimer protein.

40. (New) The method of claim 39, wherein the candidate compound is a peptide or polypeptide.

41. (New) A method for determining the crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein, wherein the E2NT dimer protein and any of its mutations is mapped onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and the effect of mutations on folding of the E2 protein.

REMARKS

Please note that the claims pending at the time of this filing are the claims of the international application serial no. PCT/GB00/03568, *i.e.* claims 1-33. Claim 33 has been cancelled and claims 34-41 have been added. The pending claims have been amended above to better conform to United States practice. The marked-up version of the changes to the specification and claims are attached hereto in the "Version With Markings to Show Changes Made".

It is respectively submitted that this application is now in condition for substantive examination, which action is respectfully requested.

Respectfully submitted,

Jarett K. Abramson
Attorney for Applicants
Registration No. 47,376

Enc: Version With Markings to Show Changes Made

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Susan E. Freedman
Date of Signature: March 15, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims have been amended as follows:

2. (Amended) [An] The E2NT dimer protein [according to] of Claim 1 wherein the residues lie on opposite sides of an N-terminal domain.

3. (Amended) [An] The E2NT dimer protein [according to either preceding claim] of Claim 1, wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer.

4. (Amended) [An] The E2NT dimer protein [according to] of Claim 3 comprising three clusters.

5. (Amended) [An] The E2NT dimer protein [according to either of Claims] of Claim 3 [or 4] wherein a first cluster of vital residues is associated with interactions between N1 and N2 domains and comprises any one or more of the following residues: Ile82, Glu90, Trp92, Lys112, Tyr138, Val145.

6. (Amended) [An] The E2NT dimer protein [according to any one of Claims 3-5] of Claim 3, wherein a second cluster of residues is associated with N1 interactions and comprises either or both of residues Trp33 and Leu94.

7. (Amended) [An] The E2NT dimer protein [according to any one of Claims 3-6] of Claim 3, wherein a third cluster of residues is associated with N2 interactions and comprises any one or more of the following residues: Pro106, Lys111, Phe168, Trp134.

8. (Amended) [An] The E2NT dimer protein [according to any preceding claim] of Claim 1, further comprising residues associated with transactivation and/or replication properties of E2.

9. (Amended) [An] The E2NT dimer [according to] of Claim 8, wherein the residues comprise any one or more of the following residues: Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69.

10. (Amended) [Use of a] A method for determining the structure of a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein, [according to any preceding claim or homologue thereof in mapping mutations] wherein the E2NT dimer protein and any of its mutations are mapped onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and the effect of mutations on folding of the E2 protein.

11. (Amended) [Use] The method according to Claim 10 in rationalised antiviral drug design.

12. (Amended) [An *in vitro*] A method for identifying and/or selecting a candidate therapeutic agent, the method comprising:

determining interaction of a E2 N-terminal module (E2NT) dimer in a sample by contacting said sample with said candidate therapeutic agent and measuring DNA loop formation in E2 *in vitro*.

13. (Amended) [Use of the] The method according to Claim 12 [in] further comprising identifying and/or selecting an antiviral candidate therapeutic agent.

14. (Amended) [Use according to] The method according to Claim 13, wherein [identification/selection] the identifying and/or selecting of the antiviral candidate therapeutic agent depends on its ability to interfere with or block interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.

15. (Amended) [Use of an E2NT dimerisation inhibitor for the preparation of a medicament for treatment of conditions that arise as a result of] A method of treating an HPV infection in a subject comprising:

introducing an E2NT dimerisation inhibitor in said subject.

16. (Amended) [Use] The method according to Claim 15 [for the treatment of] further comprising treating warts, proliferative skin lesions and/or cervical cancer.

18. (Amended) Use of a dimerisation surface of an crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof according to [any one of Claims 1-9] Claim 1 as a target site for interaction with putative antiviral agents and/or for measuring efficacy of said agents.

20. (Amended) [A] The method of claim 19, wherein the method by which the E2NT crystal structure is obtainable comprises crystallisation using hanging-drop vapour diffusion.

21. (Amended) [A] The method of claim 19, [or claim 20] wherein the method by which E2NT crystal structure is obtainable comprises X-ray diffraction using uranium acetate and gold cyanide E2NT derivatives and refining with data extending to 1.9 Å spacing.

22. (Amended) [A] The method of [any of claims] Claim 19 [to 21], wherein the crystal structure comprises the portions of amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94.

23. (Amended) [A] The method of [any of claims] Claim 19 [to 22], wherein the rationalised drug design comprises designing drugs which interact with the dimerisation surface of E2NT.

32. (Amended) A method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex [according to claim 27 or claim 28] comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3 or a homologue of said molecule or

molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

a. employing computational means to perform a fitting operation between the chemical entity and a dimerisation surface of the molecule or molecular complex; and

b. analysing the results of said fitting operation to quantify the association between the chemical entity and the dimerisation surface.

Claim 33 has been canceled without prejudice or disclaimer.

13/prts

Target for Antiviral Therapy

The present invention provides a crystallised module of a nuclear phosphoprotein and an assay and method for determining interactions with human papillomavirus E2 for use in drug design, for use particularly but not exclusively in designing antiviral agents with potential use in treating warts, proliferative skin lesions and carcinoma of the cervix.

Background to the Invention

Human papillomaviruses (HPVs) cause warts and proliferative lesions in skin and other epithelia. In a minority of HPV types ("high risk", which include HPVs 16, 18, 31, 33, 45 and 56), further transformation of the wart lesions can produce tumours, most notably carcinoma of the cervix[1]. HPVs have evolved a sophisticated system of control, mediated by protein:DNA and protein:protein interactions, that involves both cellular and viral proteins. The 45 kDalton nuclear phosphoprotein, E2, has two central roles in this control. It acts as the principal virally encoded transcription factor and, in association with the viral E1 protein, it creates the molecular complex at the origin of the viral DNA replication[2].

E2 has three distinct modules. The N-terminal module (E2NT) of about 200 amino acids is responsible for interactions with viral and host cell transcription factors. It is followed by a flexible, proline-rich, linker module and a C-terminal module (E2CT), each of about 100 amino acids [3] (Fig. 1a). The E2CT binds as a homodimer to DNA sites with a consensus sequence of $ACCGN_4CGGT$ [4]. In most HPVs a long upstream regulatory region (URR) precedes the viral genes and contains four spatially conserved E2 binding sites: three sites proximal to the transcription start site (p97 in HPV16) and one approximately 500bp upstream.

The dimer of E2CT serves to anchor E2 protein to its recognition sites on the DNA, the function of the E2NT is to bind and localise at least three cellular transcription

factors, Sp1, TFIIB and AMF-1, to the transcription initiation complex. In addition, E2 interacts with another viral protein, E1, which has ATPase and helicase activities. E1 itself binds to the viral origin of replication which consists of about 100 bp and is surrounded by the three E2-binding sites, proximal to the transcription start. The E2:E1 interaction greatly increases the rate of HPV genome replication[2,5,6], Fig. 1a. An intact E2 is essential for the normal productive (wart) life cycle of HPV, however during malignant progression HPV DNA is integrated into the host cell genome, which usually results in disruption of the E2/E1 ORFs and loss of E2 protein, in turn leading to dysregulated expression of the viral oncogenes E6 and E7[7].

Consistent with its role as a transcription regulator, E2 has been shown to direct the formation of loops in DNA containing E2 binding sites[8]. The loops were only formed with intact E2, and not with the E2CT alone. The E2 binding sites did not function independently and their co-operative effect was mediated by full length E2, leading the authors to suggest that there were specific interactions mediated by E2 that bridged across the set of DNA binding sites through its N-terminal. A similar DNA loop structure could also be achieved with Sp1, a cellular transcription factor, which forms a complex with distally bound E2 [9]; Sp1/E2 interactions are critical for transcription activation in BPV[10].

Eighty six known E2 proteins from different species and different human subtypes[11] are highly conserved, with sequence identities typically of 35% in the N and C-terminal modules (Fig. 1b). The crystal structure of the E2CT has been determined both alone and in complex with cognate DNA[12-14]. The module is a dimer with a barrel fold, and induces substantial bending (42-44°) of the DNA from its B-form double helix[14].

The structure of the proteolytic fragment of HPV18 E2NT, missing 65 N-terminal residues, was recently reported at 2.1 Å spacing[15]. This allowed some analysis of mutational effects on function, although the missing 65 amino acids contain residues which are essential for the transcriptional and replication activities of the protein.

We report herein the structure of the complete E2NT determined by X-ray analysis at 1.9 Å. We have found that it is an L-shaped molecule with the residues vital for transcriptional and replication activities of the protein lying on opposite sides of the N-terminal domain. Surprisingly, our results show that the surface, vital for transcription activation, is in fact involved in association of two E2NT's into a dimer. We suggest that dimerisation of E2NT plays an important and key role in induction of DNA loop formation, the mechanism by which distally bound transcription factors would be brought close to the site of transcription initiation. More importantly, our results raise the possibility that dimer formation serves as a molecular switch between early gene expression and viral genome replication during HPV infection.

The process of rationalised drug design requires no explanation or teaching for the skilled person but a brief description is given here of computational design for the lay reader: various computational analyses are necessary to determine whether a molecule is sufficiently similar to the target moiety or structure. Such analyses may be carried out in current software applications, such as the Molecular Similarity application of QUANTA (Molecular Simulations Inc., Waltham, Mass.) version 3.3, and as described in the accompanying User's Guide, Volume 3 pages. 134-135.

The Molecular Similarity application permits comparisons between different structures, different conformations of the same structure, and different parts of the same structure. The procedure used in Molecular Similarity to compare structures is divided into four steps: 1) load the structures to be compared; 2) define the atom equivalences in these structures; 3) perform a fitting operation; and 4) analyze the results.

Each structure is identified by a name. One structure is identified as the target (i.e., the fixed structure); all remaining structures are working structures (i.e., moving structures). When a rigid fitting method is used, the working structure is translated and rotated to obtain an optimum fit with the target structure. The fitting operation uses a least squares fitting algorithm that computes the optimum translation and

rotation to be applied to the moving structure, such that the root mean square difference of the fit over the specified pairs of equivalent atom is an absolute minimum. This number, given in angstroms, is reported by QUANTA.

One skilled in the art may use one of several methods to screen chemical entities or fragments for their ability to associate with a target. Again, these methods require no elucidation for the skilled person but are described here for the benefit of the unskilled reader. The screening process may begin by visual inspection of the target on the computer screen, generated from a machine-readable storage medium. Selected fragments or chemical entities may then be positioned in a variety of orientations, or docked, within that binding pocket as defined supra. Docking may be accomplished using software such as Quanta and Sybyl, followed by energy minimization and molecular dynamics with standard molecular mechanics force fields, such as CHARMM and AMBER.

Specialized computer programs may also assist in the process of selecting fragments or chemical entities. These include:

1. GRID (P. J. Goodford, "A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules", J. Med. Chem., 28, pp. 849-857 (1985)). GRID is available from Oxford University, Oxford, UK.

2. MCSS (A. Miranker et al., "Functionality Maps of Binding Sites: A Multiple Copy Simultaneous Search Method." Proteins: Structure, Function and Genetics, 11, pp. 29-34 (1991)). MCSS is available from Molecular Simulations, Burlington, Mass.

3. AUTODOCK (D. S. Goodsell et al., "Automated Docking of Substrates to Proteins by Simulated Annealing", Proteins: Structure, Function, and Genetics, 8, pp. 195-202 (1990)). AUTODOCK is available from Scripps Research Institute, La Jolla, Calif.

4. DOCK (I. D. Kuntz et al., "A Geometric Approach to Macromolecule-Ligand Interactions", J. Mol. Biol., 161, pp. 269-288 (1982)). DOCK is available from University of California, San Francisco, Calif.

Once suitable chemical entities or fragments have been selected, they can be assembled into a single compound or complex. Assembly may be preceded by visual inspection of the relationship of the fragments to each other on the three-dimensional image displayed on a computer screen in relation to the structure coordinates of calcineurin. This would be followed by manual model building using software such as Quanta or Sybyl.

Useful programs to aid one of skill in the art in connecting the individual chemical entities or fragments include:

1. CAVEAT (P. A. Bartlett et al, "CAVEAT: A Program to Facilitate the Structure-Derived Design of Biologically Active Molecules". In Molecular Recognition in Chemical and Biological Problems", Special Pub., Royal Chem. Soc., 78, pp. 182-196 (1989)). CAVEAT is available from the University of California, Berkeley, Calif.

2. 3D Database systems such as MACCS-3D (MDL Information Systems, San Leandro, Calif). This area is reviewed in Y. C. Martin, "3D Database Searching in Drug Design", J. Med. Chem., 35, pp. 2145-2154 (1992).

3. HOOK (available from Molecular Simulations, Burlington, Mass.).

As the skilled reader will already know, instead of proceeding to build ligand for the target in a step-wise fashion, one fragment or chemical entity at a time as described above, inhibitory or other target-binding compounds may be designed as a whole or *de novo*. These methods include:

1. LUDI (H.-J. Bohm, "The Computer Program LUDI: A New Method for the De Novo Design of Enzyme Inhibitors", J. Comp. Aid. Molec. Design, 6, pp. 61-78 (1992)). LUDI is available from Biosym Technologies, San Diego, Calif.

2. LEGEND (Y. Nishibata et al., Tetrahedron, 47, p. 8985 (1991)). LEGEND is available from Molecular Simulations, Burlington, Mass.

3. LeapFrog (available from Tripos Associates, St. Louis, Mo.).

Other molecular modelling techniques may also be employed. See, e.g., N. C. Cohen et al., "Molecular Modeling Software and Methods for Medicinal Chemistry, J. Med. Chem., 33, pp. 883-894 (1990). See also, M. A. Navia et al., "The Use of Structural Information in Drug Design", Current Opinions in Structural Biology, 2, pp. 202-210 (1992).

Once a compound has been designed or selected by the above methods, the efficiency with which that entity may bind to a target may be tested and optimized by computational evaluation. For example, an effective ligand will preferably demonstrate a relatively small difference in energy between its bound and free states (i.e., a small deformation energy of binding). Thus, the most efficient ligands should preferably be designed with a deformation energy of binding of not greater than about 10 kcal/mole, preferably, not greater than 7 kcal/mole. Ligands may interact with the target in more than one conformation that is similar in overall binding energy. In those cases, the deformation energy of binding is taken to be the difference between the energy of the free entity and the average energy of the conformations observed when the inhibitor binds to the protein.

An entity designed or selected as binding to a target may be further computationally optimized so that in its bound state it would preferably lack repulsive electrostatic interaction with the target enzyme. Such non-complementary (e.g., electrostatic) interactions include repulsive charge-charge, dipole-dipole and charge-dipole

interactions. Specifically, the sum of all electrostatic interactions between the inhibitor or other ligand and the target, when the inhibitor is bound to the target, preferably make a neutral or favourable contribution to the enthalpy of binding.

Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interaction. Examples of programs designed for such uses include: Gaussian 92, revision C [M. J. Frisch, Gaussian, Inc., Pittsburgh, Pa. .COPYRGT.1992]; AMBER, version 4.0 [P. A. Kollman, University of California at San Francisco, .COPYRGT.1994]; QUANTA/CHARMM [Molecular Simulations, Inc., Burlington, Mass. .COPYRGT.1994]; and Insight II/Discover (Biosysm Technologies Inc., San Diego, Calif. .COPYRGT.1994). These programs may be implemented, for instance, using a Silicon Graphics workstation, IRIS 4D/35 or IBM RISC/6000 workstation model 550. Other hardware systems and software packages will be known to those skilled in the art.

Once the ligand has been optimally selected or designed, as described above, substitutions may then be made in some of its atoms or side groups in order to improve or modify its binding properties. Generally, initial substitutions are conservative, i.e., the replacement group will have approximately the same size, shape, hydrophobicity and charge as the original group. It should, of course, be understood that components known in the art to alter conformation should be avoided. Such substituted chemical compounds may then be analyzed for efficiency of fit to a calcineurin-like binding pocket by the same computer methods described in detail, above. Again, all these facts are familiar to the skilled person.

Another approach is the computational screening of small molecule data bases for chemical entities or compounds that can bind in whole, or in part, to a target. In this screening, the quality of fit of such entities to the binding site may be judged either by shape complementarity or by estimated interaction energy. E. C. Meng et al., J. Comp. Chem., 13, pp. 505-524 (1992).

The computational analysis and design of molecules, as well as software and computer systems therefor are described in US Patent No 5,978,740 which is included herein by reference, including specifically but not by way of limitation the computer system diagram described with reference to and illustrated in Fig 3 thereof as well as the data storage media diagram described with reference to and illustrated in Fig 4s and 5 thereof.

Statement of the Invention

According to a first aspect of the invention there is provided a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof, for use in rationalised drug design. We have found that the dimer comprises residues vital for transcriptional and replicational activities of said protein lying on opposite sides of an N-terminal domain, for use in rationalised drug design.

Preferably the E2NT dimer protein is substantially as depicted in any of Figures 2c and/or 3a-d.

According to a second aspect of the invention there is provided an *in vitro* method for identifying and/or selecting a candidate therapeutic agent, the method comprising determining interaction of a E2 N-terminal module (E2NT) dimer in a sample by contacting said sample with said candidate therapeutic agent and measuring DNA loop formation.

Preferably, the method is for use in identifying and/or selecting an antiviral candidate therapeutic agent.

Preferably, the candidate therapeutic agent interferes or blocks interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.

According to a third aspect of the invention there is provided use of an E2NT dimerisation inhibitor in the preparation of a medicament for use in treating warts, proliferative skin lesions and/or cervical cancer.

According to a fourth aspect of the invention there is provided a method of monitoring the efficacy of an antiviral therapy in a patient receiving a medicament for the treatment of warts, proliferative skin lesions and/or cervical cancer comprising taking a sample from said patient and measuring E2NT interactions and/or DNA loop formation.

Thus it will be appreciated that a patient can be monitored at the start of therapy to test its effectiveness. Alternatively, a patient can be monitored once a therapy has been established so as to monitor its efficacy with a view to altering a therapy if found to be unsatisfactory.

The human papillomavirus E2 protein controls the primary transcription and replication of the viral genome. Both activities are governed by a ~200 amino acid N-terminal module (E2NT) which is connected to a DNA binding C-terminal module by a flexible linker. The crystal structure of the E2NT module from high-risk type 16 human papillomavirus reveals an L-shaped molecule with two closely packed domains, each with a novel fold. It forms a dimer in the crystal and in solution. The dimer structure is important in the interactions of E2NT with viral and cellular transcription factors and is the key to induction of DNA loops by E2. These loops may serve to target distal DNA-binding transcription factors to the region proximal to the start of transcription. The structure has implications for antiviral drug design and cervical cancer therapy.

The invention includes method for identifying and/or selecting a candidate therapeutic agent, comprising applying rationalised drug design to a crystal structure obtainable by crystallising E2NT, cryogenically freezing the crystals and generating the crystal structure using X-ray diffraction. The method by which the E2NT crystal

structure is obtainable may comprise crystallisation using hanging-drop vapour diffusion. The method by which E2NT crystal structure is obtainable may comprise X-ray diffraction using uranium acetate and gold cyanide E2NT derivatives and refining with data extending to 1.9 Å spacing. The crystal structure may comprise the portions of amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94. The rationalised drug design may comprise designing drugs which interact with the dimerisation surface of E2NT.

Further provided is a computer for producing a three-dimensional representation of a molecule or molecular complex, wherein said molecule or molecular complex comprises or a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å , wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3;

(b) a working memory for storing instructions for processing said machine-readable data;

(c) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

(d) a display coupled to said central-processing unit for displaying said three-dimensional representation.

In class of embodiments, the three-dimensional representation is of a molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or wherein said three-dimensional representation is of a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

An additional aspect of the invention resides in a computer for determining at least a portion of the structure coordinates corresponding to an X-ray diffraction pattern of a molecule or molecular complex, wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structural coordinates according to Table 3;

(b) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises an X-ray diffraction pattern of said molecule or molecular complex;

(c) a working memory for storing instructions for processing said machine-readable data of (a) and (b);

(d) a central-processing unit coupled to said working memory and to said machine-readable data storage medium of (a) and (b) for performing a Fourier transform of the machine readable data of (a) and for processing said machine readable data of (b) into structure coordinates; and

(e) a display coupled to said central-processing unit for displaying said structure coordinates of said molecule or molecular complex.

A yet further aspect of the invention relates to a crystallised molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT

amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å. The molecule or molecular complex may be defined by the set of structure coordinates according to Table 3, or a homologue thereof, wherein said homologue has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

27. A machine-readable data storage medium (e.g. a magnetic or optical storage medium, for example a hard disc, a floppy disc or a CD-ROM), comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

In the machine-readable data storage medium the molecule or molecular complex may be defined by the set of structure coordinates according to Table 3, or a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

The invention further provides a machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second

set of machine readable data, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates according to Table 3; and said second set of data comprises an x-ray diffraction pattern of a molecule or molecular complex.

In another aspect, the invention resides in a method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex according to the invention, comprising the steps of:

a. employing computational means to perform a fitting operation between the chemical entity and a dimerisation surface of the molecule or molecular complex; and

b. analysing the results of said fitting operation to quantify the association between the chemical entity and the dimerisation surface.

Detailed Description of the Invention

The invention will now be described by way of example only with reference to the following Figures and Tables wherein:

Table 1 illustrates X-ray data and phasing statistics;

Table 2 illustrates refinement and model correlation;

Table 3 shows the structure coordinates of the E2NT module;

Figure 1a represents functional assignments of HPV 16 E2 protein;

Figure 1b illustrates sequence alignment of E2NT modules from a subset of HPV types;

Figure 2a illustrates a stereo view of electron density with a final model at the dimer interface of the E2NT module, viewed down the crystallographic two-fold axis;

Figure 2b represents a stereo ribbon diagram of the E2NT module;

Figure 2c represents the E2NT dimer;

Figure 3a illustrates a schematic view of URR;

Figure 3b illustrates a schematic view of loop formation induced by binding of E2 proteins to two cognate sites;

Figure 3c illustrates a model of E2 dimer formation;

Figure 3d illustrates loops within URR as shown in Figure 3b;

Figure 4a illustrates the distribution of conserved residues on the E2NT monomer;

Figure 4b illustrates a first cluster of conserved residues on the E2NT monomer;

Figure 4c illustrates a second cluster of conserved residues on the E2NT monomer; and

Figure 4d illustrates conserved residues Gln12 and Glu39.

Those of skill in the art understand that a set of structure coordinates for an enzyme or an enzyme-complex or a portion thereof, is a relative set of points that define a shape in three dimensions. Thus, it is possible that an entirely different set of coordinates could define a similar or identical shape. Moreover, slight variations caused by acceptable errors in the individual coordinates will have little, if any effect on overall shape. In terms of binding pockets, these acceptable variations would not be expected to alter the nature of ligands that could associate with those pockets.

The term "associating with" refers to a condition of proximity between a chemical entity or compound, or portions thereof, and a calcineurin molecule or portions thereof. The association may be non-covalent--wherein the juxtaposition is energetically favored by hydrogen bonding or van der Waals or electrostatic interactions--or it may be covalent.

The invention is also described with reference to US Patent No 5,978,740 which is included herein by reference, including specifically but not by way of limitation the computer system diagram described with reference to and illustrated in Fig 3 thereof as well as the data storage media diagram described with reference to and illustrated in Fig s 4 and 5 thereof.

With reference to Figure 1a and functional assignments of E2. There is shown in a schematic view of NT, linker and CT modules of E2 indicating known functions of each module. Amino acid numbers which delimit the modules correspond to E2 from HPV16. In Figure 1b, there is shown the sequence alignment of the E2NT modules from a subset of HPV types (HPV16, HPV18, HPV11 and HPV2a) and one BPV type. Shaded blocks above the alignment indicate the experimentally determined secondary structure. Shaded blocks below the sequences indicate the minimal peptide sequences involved in protein:protein interactions, suggested by mutation studies. Residues with more than 90% identity among 86 PV types are coloured: red for internal structural residues, green for residues within the fulcrum region, blue for surface residues.

With reference to the structural features of E2, in Figure 2a there is shown a stereo view of the electron density with the final model, at the dimer interface of the E2NT module, viewed down the crystallographic two-fold axis. The likelihood weighted map is contoured at the 1.5 σ level. Ribbons of two independent monomers are coloured blue and yellow. Side chains of ARG37 and Ile73 which are known to be critical for transactivation [4,31] , are shown in dark green; side chain of other residues at the dimer interface are shown in light green. Oxygen atoms are in red, nitrogen in blue, water molecules are shown as orange spheres and hydrogen bonds as dashed sticks. In Figure 2b, there is shown a stereo ribbon diagram of the E2NT module. The N1 domain is shown in aquamarine and the N2 domain in pink, with the fulcrum in green. In Figure 2c, there is shown the dimer of E2NT, showing the extent of the interface between the two subunits. The view is as in Figure 2a but rotated clockwise by 90°. Side chains of Gln12 and Glu39 which are critical for interactions with E1 [31-33,37] are shown in magenta. Side chains of residues at the dimer interface are coloured as per Figure 2a.

With reference to Figures 3a-d there is shown loop formation in the URR of HPV16. In Figure 3a, there is shown a schematic view of the URR. The four E2-binding sites are represented by boxes. Numbers in italics indicate distances between individual

sites upstream of the p97 promoter. Two possible E2 configurations, with separate or dimeric E2NT modules are shown. In Figure 3b, there is shown a schematic view of loop formation induced by binding of E2 proteins to two cognate sites, based on the experiments reported by Knight *et al*[8]. In Figure 3d, there is shown the possible DNA loops within the URR as depicted in Figure 3b. In Figure 3c, there is shown a model of the formation of E2 dimers, showing interactions between both the C-terminal and E2NT modules. The C-terminal dimer, with its bound DNA, is based on the crystal structure of this module[12]. The E2NT dimer is proposed from the present work. The relative orientation and position of the E2NT and C-terminal modules is purely schematic.

With reference to Figures 4a-d there are shown functionally important residues. In Figure 4a, there is shown the distribution of conserved residues on the E2NT monomer. In Figures 4b and 4c there is shown the two clusters of conserved residues in the fulcrum of E2NT. In Figure 4d, there are shown conserved residues Gln12 and Glu39. Bonds in ball-and stick models are coloured aquamarine (N1 domain), pink (N2 domain) and green (fulcrum). Hydrogen bonds are shown as dashed lines, water molecules as orange spheres, oxygen atoms are in red, nitrogen atoms in blue and sulphur atoms in yellow.

There is convincing evidence that the E2 protein has an extended structure, is flexible and that its functions depend on this property. This is probably the reason why the intact protein has not yet been crystallised in spite of intensive efforts. A major problem is the extended flexible linker module, with around 100 residues. E2NT proved difficult to crystallise, and a number of different constructs were made and overexpressed before crystallisation with residues 1 to 201 was achieved, but even this construct possessed limited stability. The protein had to be crystallised within 2-3 days of purification; crystals grew within about 48 hours but only retained useful diffraction quality for a further 2-3 days. This necessitated that crystals be rapidly vitrified in cryoprotectant buffer and stored for use as soon as detector time became available[16].

Crystals of E2NT belong to the space group $P3_121$ with unit-cell dimensions a=b=54.3 Å, c=155.5 Å. The structure was determined using two heavy atom derivatives and refined with data extending to 1.9 Å spacing (Fig. 2a). The main chain is well defined throughout with the exception of residues 125 and 126 which are in an exposed loop and are mobile. There was density for the last residue of the His-tag at the N-terminus, but none for the remainder of this entity. All amino acids lie in the allowed regions of the Ramachandran (ϕ,ψ) plot[17] with 92.4% in most favoured regions[18].

The transactivation module is composed of two domains, N1 and N2, arranged so as to give it an overall L-shaped appearance. Analysis of the PDB[19] using DALI[20] shows that both have unique organisation of their secondary structures. Domain N1, which forms the N-terminus of the intact E2, is composed of residues 1 to 92, which fold into three long α-helices, Figure 2 (b,c). There is a tight loop between α1 and α2 and a more extended one between α2 and α3. The three helices pack antiparallel to one another in the form of a twisted plane, with angles of about 20° and 25° between the pairs of consecutive helices. DALI indicated a maximum Z-score of 5.7, that could suggest a significant correlation, for colicin 1a, a membrane protein which contains three 80 Å long α-helices arranged more or less coplanar[21]. This is the only other known protein that contains a true domain made up of such a packing of three helices. In addition there were 42 other structures which gave Z-scores above 4.0, most of which were four helix bundles, such as bacterioferritin[22]. However, in these only two of the three N1 helices superimposed simultaneously on two, not always adjacent, bundle helices as a result of a more planar arrangement of helices within N1. The indications are that the similarities observed reflect the optimum stacking angle of antiparallel helices against one another rather than suggesting a common ancestor for the evolution of these molecules.

Domain N2 is made up of residues 110 to 201 and is composed almost entirely of antiparallel β structure, with only one short helical segment from residues 171 to 178,

Figure 2 (b,c). The secondary structure has two short three and four stranded antiparallel β pleated sheets interconnected by two stranded β ribbons. For this domain DALI failed to identify any significant homologies to known structures, with a highest Z-score of only 2.1. From the analysis of Harris and Botchan[15] and the present study, the N2 fold appears to be novel.

The structure between the N1 and N2 domains (residues 93 to 109) contains two consecutive single turns of helical structure, resulting in a compact and tight turn. It packs closely against elements of both domains and is not a truly independent structural domain. Rather it forms a fulcrum in the L-shape formed by N1 and N2 where it could act as a hinge, allowing the two domains to change their relative conformation in a specific way. Several of the interactions between adjacent regions of chain in the fulcrum are mediated indirectly through H-bonds involving water molecules, suggesting the possibility of flexibility.

One of the most striking features of the crystal structure is the association of two E2NT monomers into a tight dimer. The two E2NT monomers pack around the crystallographic 2-fold axis, as shown in Figure 2a. The dimer interface is formed mostly by amino acids from helices α2 and α3 of the N1 domain and by residues 142-144 from the N2 domain. The total buried surface area between the two E2NT is 2026 $A^{\circ 2}$, comparable to the 2444 $A^{\circ 2}$ buried between the two E2CT[12], which are known to form a tight dimer with a K_d of 3-6 x 10^{-8} M [23,24].

In the E2NT dimer interface, each subunit contributes a cluster of seven equivalent residues, invariant or conserved in the 86 known sequences of E2[11], with many direct and water-mediated hydrogen bonds and rather few non-polar contacts, Fig. 2. Analysis of the dimer forming surfaces shows that all the direct hydrogen bonds between monomers are made through these seven amino acids. For the invariant Arg37, all possible side-chain hydrogen bonds are made and all are well defined, Figure 2. Three of them are across the dimer interface. One hydrogen bond is critical, from NH2 to the main chain carbonyl oxygen of Leu77. A second hydrogen bond from NH2 is to OG1 of Thr81; in five out of 86 sequences this residue is

glutamine, and modelling shows a hydrogen bond is possible to the NE of Arg37. The NH1 of Arg71 H-bonds to the OE1 of residue 80, which is Glu or Gln in all but six variants. At the NE of Arg37 there is an ideal H-bond to water that itself makes another strong H-bond across the dimer interface to the main-chain carbonyl oxygen of residue 142. The role of the invariant Ile73 is the filling of the intersubunit non-polar volume made up of the aliphatic parts of Arg37, Gln76 and of Leu77 - in this case from both monomers. The Leu77 is in a few sequences substituted by valine or isoleucine and in 9 out of 86 known sequences by methionine. Inspection of the structure shows that Leu77 is partially exposed to the solvent and therefore different hydrophobic side chains could be easily accommodated at this site. Another important non-polar side chain is Ala69. Its side chain methyl packs into the surface of the other monomer at van de Waals distance from the main chain of residue 142. The only observed mutation of Ala69 is to Gly, and is easily accommodated. Gln76 is conserved or has homologous substitutions in about 2/3 of E2 sequences; in about 1/4 of the sequences there is methionine or valine at this position[11]. Although hydrophobic substitutions of Gln76 would disrupt the hydrogen bonding to Glu80 across the dimer interface, and to Arg37 from the same subunit, the hydrophobic side chain at residue 76 could instead make a compensating hydrophobic interaction with the adjacent intersubunit hydrophobic pocket formed by Ile73 and Leu77.

Modelling of the amino acid variations in the 86 known papillomavirus E2 proteins into the other contacts at the dimer interface shows that they generally can be accommodated (data not shown). The consistency of the hydrogen bonds and van de Waals contacts at the monomer-monomer interface in the various sequences suggests therefore that the E2NT dimer interactions are potentially present in all papillomaviruses.

The first experimental evidence for the E2NT dimerisation in the presence of DNA with multiple E2-binding sites was provided by Knight *et al* in 1991[8]. Their studies showed that intact E2 led to the formation of DNA loops on templates with widely separated E2 binding sites, while a truncated E2, containing the DNA-binding E2CT but missing the N-terminal 161 residues, did not. Such dimerisation is further

supported by the observed synergistic transcription activation by a complex of two DNA-bound E2 dimers[25].

To analyse the functional behaviour of the E2NT dimers further, we measured the dissociation constant by sedimentation equilibrium using analytical ultracentrifugation of recombinant E2NT protein containing the 201 N-terminal amino acids. A value of $K_d = 8.1 \pm 4 \times 10^{-6}$ M was obtained, indicating medium-strength association. The micromolar range of the E2NT dimer K_d is certainly physiologically significant, and compares well with values for other transcription factors which have relatively low dissociation constants, often with the K_d values between 1 μM and 20 μM [26,27]. *In vivo*, the interaction could be enhanced when the two E2NT modules are placed in close proximity. Indeed, E2CT forms dimers which bind to the multiple DNA-binding sites located within the URR of viral DNA with K_d of protein:DNA interactions usually in the nanomolar range[28]. Consequently, the local concentration of E2NT, bound to the E2CT via the non-conserved, flexible ~80 amino-acid linker, is effectively increased.

E2NT dimer interactions, as seen in the crystal structure, could form either between modules which are already part of a single E2 dimer, formed as a result of E2CT dimerisation interactions and bound to a single E2 binding site on the DNA (Fig. 3a), or between two preformed E2 dimers located on different E2 binding sites (Fig. 3b). The results of the electron microscopy suggest that the latter dimerisation does occur[8]. Although no direct experimental evidence exists for the former dimerisation, it does also seem possible due to the flexibility of the linker connecting the two modules. We propose that E2 molecules may initially keep their N-terminal modules within their internal dimers, but swap N-terminal modules and cross link to E2 molecules bound to distant DNA binding sites to form active loop structures during transcriptional activation and / or HPV DNA replication (Figure 3d). As discussed below, the effects of mutations on transcriptional transactivation can be explained in terms of the dimer being an essential element in this process.

E2 is a regulator of both transcription and viral DNA replication and thus interacts with other viral and host macromolecules in the infected cell. Indication of the possible importance of individual residues in the function comes firstly from the structure, secondly from the extensive set of sequences of the papillomaviral E2's and thirdly from mutagenesis studies on the individual proteins. In the following we make a primary attempt to map the molecule's function onto its structure.

The pattern of amino acid conservation for the 86 available papilloma sequences[11] has been analysed using the GCG program suite[29]. The sequences exhibit striking variation, characteristic of some virus families. However, 33 of the total 201 residues in the E2NT construct were totally or highly conserved. Fig. 4a illustrates the distribution of these 33 residues in the dimer. These were categorised into two sets: those with an essentially structural role and those exposed on the surface with a potential for intermolecular interactions. Thirteen residues (Fig. 1b) are buried or play a purely structural role within the monomer, they are not expected to be of functional importance and will not be discussed here.

A further 12 of these 33 residues stand out as having a structural role in the interface of the N1 and N2 domains. They form three clusters, the first making direct interactions between the two domains (Ile82, Glu90, Trp92, Lys112, Tyr138, Val145) and two separate sets of interactions, one from N2 (Pro106, Lys111, Phe168, Trp134) and the other from N1 (Trp33, Leu94) to the structure connecting them, referred to here as a fulcrum. The first two clusters are shown in Figure 4 b, c and it can be seen that Lys111 and Lys112 play key roles. Their side chains point in opposite directions to one another and their terminal amino groups are involved in near ideal patterns of hydrogen bonds. The flat surfaces of their extended side chains stack against Trp134 and Trp92, respectively. This clustering of invariant residues at the interface indicates a functional importance for the relative orientation of N1 and N2. The fulcrum could indeed provide a flexible pivot between the two domains, but there is no direct evidence for this as yet. Finally, while the side chain of Glu90 is held tightly in place by two H-bonds and could have a structural role, its OE2 atom is

exposed on the surface and is surrounded by near invariant side-chains, which may thus play a part in interactions with other molecules.

Of the remaining eight conserved residues, mutational substitutions of Glu20, Glu100 and Asp122 [30-33] had moderate effects on the transactivation and replication properties of E2, which depended on a particular viral strain. Glu20 lies on the top surface of N1. Asp122 lies far away on the distal surface of N2. Glu100 is completely exposed and points into the solvent at the junction of the L between the N1 and N2 domains. The functional role of these amino acids has yet to be clarified.

Three conserved amino acids (Arg37, Glu39 and Ile73) have been subjected to point mutation and the effects on the two principal functions of E2, i.e. transactivation and HPV DNA replication have been assessed (reviewed in[4],also [31,34,35]). Together with the remaining two conserved amino acids, Gln12 and Ala69, these residues form two functionally important surfaces (see below).

Finally, a number of the mutational results (reviewed in [4], also [31,34,35]) correspond to residues that can be assigned to structural roles. Substitution of these residues will lead to substantial conformational changes and a probable inability to fold correctly. This is particularly true for some of the deletion mutants involving the core of the molecule. Knowledge of the structure will allow a more rational choice and design of mutants in the future.

The induction of DNA loops by E2NT dimerisation could be important for the construction of the active transcription bubble by targeting DNA-binding transcription factors, bound at distal sites, to the region proximal to the start of transcription (reviewed in [36]). In support of this, residues Arg37, Ile73 and Gln76 map onto the surface of E2NT involved in dimer formation, and mutations result in considerable disruption of transactivation, while having little effect on replication, [4,15,31]. The structure also shows that Ala69 which points its side chain methyl across the dimer interface, is also critical for transactivation. Mutational substitutions to

amino acids with longer side chains should have a knock out effect on E2NT dimer formation and consequently on transactivation.

The sites of association with cellular transcription factors AMF-1 (residues 74-134) and TFIIB (134-216) were previously mapped onto the E2NT module (Figure 1) using a series of deletion mutants as well as point mutations[34,35]. These sites were mutually exclusive. In the structure, residues 74-134 include the fulcrum, while residues 134-216 correspond to domain N2. Further biochemical and structural studies can now be planned to characterise these interactions in more detail.

Replication of the viral genome is initiated by binding of another viral protein, E1, to the origin of DNA replication[4] which is itself flanked by two E2 binding sites, Fig. 3a. While the function of E2CT dimers is to bind specifically to the DNA sites, E2NT interaction with E1 enhances the binding of E1 to this region. Mutational substitutions of Glu39 generally retained transcriptional activation while DNA replication was substantially reduced[31-33,37]. In the structure, the conserved Glu39 makes every possible hydrogen bond by its side chain carboxyl oxygens, Fig. 4d. One hydrogen bond is to NE2 of Gln12, which is absolutely conserved in all known sequences of E2. The other three hydrogen bonds are to the water molecules which are part of an intimate net of well-defined water molecules surrounding Glu39 and mediating its interactions with adjacent residues. Interestingly, a number of these protein interactions with water molecules are conserved as they are made to the protein backbone, including carbonyl oxygens of Gln12, Met36 and Lys68. While mutation of Gln12 in BPV1 only slightly affected both transactivation and replication, it substantially reduced cooperative origin binding[30,32]. The close positioning of Gln12 and Glu39 in the three-dimensional structure further enhances the notion that these two resides are involved in interactions with E1. The conserved set of interactions at Gln12/Glu39 suggests that the main chain carbonyl oxygens of Gln12 and Met36 and the conserved water molecules could be also involved in these interactions. Gln12/Glu39 are surrounded by Leu8, Ile15, Met36, Tyr43, Gln57 and

Lys68, which are unlikely to contribute into E2/E1 interactions, as these residues are not well conserved in E2 sequences from different papillomaviruses.

The Gln12/Glu39 cluster lies on a side of the N1 domain which is opposite to the side involved in transactivation (and dimerisation), Figure 2c. Notably, the spatial separation of the two functionally important surfaces suggests that E2NT module could be able to interact with E1 at the same time as it interacts through the dimerisation interface with another E2NT module.

The structure reported here for the entire E2 transactivation module, has several implications for understanding of E2 function. It is now possible to map known mutations onto the E2 three-dimensional structure, and to use the knowledge of amino acid conservation and the effects of mutations to assign roles in folding, structure and function to residues. To this end, our results indicate that molecular surfaces involved in transactivation and E1-binding are located at opposite sides of the N1 domain of E2NT, suggesting that both surfaces could be accessed simultaneously by other protein factors. In line with these observations, E1 has been shown to modulate transactivation by directly interacting with E2, leading to repression of transactivation in the presence of excess E1[38]. It is not inconceivable that the docking of E2NT dimer with E1 is sufficient to block further association with other target proteins.

The structure shows that the transactivation surface is involved in the formation of the E2NT dimer, which could cross-link E2 molecules bound by their E2CT modules to well-separated DNA sites. Inevitably, such dimerisation would cause DNA to form a loop structure, targeting distally bound transcription factors to regions close to the promoter. While this process has been suggested to be essential for transactivation[36], the definition of interacting surfaces between E2 and other cellular transcription factors requires a great deal of further study.

Our results suggest that the process of DNA loop formation could involve swapping of E2NT modules across E2 dimers bound at separated DNA sites (Fig. 3a-d). The polar components of the monomer-monomer interactions may favour such exchange. Domain swapping is a well-recognised phenomenon that occurs relatively frequently between two individual monomers containing domains connected by a flexible linker [39,40]. E2 is to our knowledge the first example where the swapping event is predicted to occur between dimers.

The dimerisation surface of E2 represents a good target for designing anti-viral drugs, since it is essential for viral transcription, there is no homologous human protein and the residues forming the interface are highly conserved among different viral strains. Dynamic interactions between transcription factors play a central role in the regulation of transcription and replication. Dimerisation, heterodimerisation and the monomer-to-dimer transition may play important roles during the control of the papillomavirus life cycle. These processes themselves can be regulated through phosphorylation, proteolysis, interaction with small ligands or changes in their intracellular concentration. It has been suggested that E2 can regulate the switch between early gene expression and viral genome replication during HPV infection[41]. It is possible that dimerisation of E2NT modules plays an essential role during this process. One scenario would be to activate transcription via induction of DNA loop formation at early stages of the viral life cycle. At later stages, when the concentration of expressed E2 proteins within the cell becomes high and comparable with the K_d for E2 dimer formation, free E2NT modules could compete for dimerisation with those involved in DNA loop formation and titrate them away, switching off transcription and stimulating replication. It is also possible that other protein factors could be involved in this process, including, for example, E1.

The invention therefore includes the use of E2NT crystal structure in the design of anti-viral drugs, since it is essential for viral transcription. In the rationalised computational design of drugs using the crystal structure, computational analyses are therefore necessary to determine whether a molecule or the E2NT-binding portion

thereof is sufficiently similar to the E2NT structure. Such analyses may be carried out in current software applications, such as the Molecular Similarity application of QUANTA (Molecular Simulations Inc., Waltham, Mass.) version 3.3, and as described in the accompanying User's Guide, Volume 3 pages. 134-135.

The Molecular Similarity application permits comparisons between different structures, different conformations of the same structure, and different parts of the same structure. The procedure used in Molecular Similarity to compare structures is divided into four steps: 1) load the structures to be compared; 2) define the atom equivalences in these structures; 3) perform a fitting operation; and 4) analyze the results.

Each structure is identified by a name. One structure is identified as the target (i.e., the fixed structure); all remaining structures are working structures (i.e., moving structures). Atom equivalency within QUANTA is defined by user input and, for the purpose of this invention equivalent atoms may be defined as protein backbone atoms (N, C.alpha., C and O) for all conserved residues between the two structures being compared. We will also consider only rigid fitting operations.

When a rigid fitting method is used, the working structure is translated and rotated to obtain an optimum fit with the target structure. The fitting operation uses a least squares fitting algorithm that computes the optimum translation and rotation to be applied to the moving structure, such that the root mean square difference of the fit over the specified pairs of equivalent atom is an absolute minimum. This number, given in angstroms, is reported by QUANTA.

For the purpose of one class of embodiments this invention, any set of structure coordinates of a molecule or molecular complex that has a root mean square deviation of conserved residue backbone atoms (N, C.alpha., C, O) of less than 1.5 .ANG. when superimposed--using backbone atoms--on the relevant structure coordinates of E2NT are considered identical. More preferably, the root mean square

deviation is less than 1.0 .ANG.. Most preferably, the root mean square deviation is less than 0.5 .ANG..

The term "root mean square deviation" means the square root of the arithmetic mean of the squares of the deviations from the mean. It is a way to express the deviation or variation from a trend or object. For purposes of this invention, the "root mean square deviation" defines the variation in the backbone of a protein from the backbone of E2NT a dimerising portion thereof, for example as defined by the structure coordinates of E2NT described herein.

The term "least squares" refers to a method based on the principle that the best estimate of a value is that in which the sum of the squares of the deviations of observed values is a minimum.

Materials and Methods

Purification and crystallisation.

Details of the purification and crystallisation of E2NT have been described previously[16]. Briefly, the ORF encoding the N-terminal 201 residues of HPV-16 E2 was cloned into the prokaryotic expression plasmid pET15b downstream of the 20-residue His-tag leader sequence; protein was expressed in *E. coli*BL21(DE3)pLysS and purified using nickel affinity and anion exchange chromatography. Crystals were obtained by hanging drop vapour diffusion with 0.8-1.2M ammonium sulphate, 0.1M triethanolamine pH 8.0-8.3 and 3-5% 2-methyl-2,4-pentanediol. Crystals grew only with very fresh protein preparations and deteriorated in terms of diffraction quality in less than a week. This necessitated freezing and storage of crystals in liquid nitrogen immediately after growth, as discussed above.

Structure determination.

All data were recorded on cryogenically frozen crystals. A native crystal was frozen for which initial data were recorded to 3.4 Å[16]. For the screening of derivatives,

crystal stability was even more limiting. Nine crystals were soaked in various heavy atom reagents immediately after growth. The crystals were screened in-house using a MAR research imaging plate on a Rigaku RU200 rotating anode source, by recording 3° of data for each and analysing the fractional isomorphous difference from the native. Three derivatives showed promising differences from the native, in the range of 15-20% after scaling using SCALEPACK[42] and were stored in liquid nitrogen. The native crystal was transported to EMBL Hamburg where 1.9 Å data were measured using synchrotron radiation from beam line X11, Table 1. In addition data were recorded at EMBL for the three promising derivatives to about 2.7 Å. Two of these derivatives proved useful in phase determination and the structure was solved by multiple isomorphous replacement with anomalous scattering (MIRAS) at 2.7 Å. The two derivatives were solved independently using the CCP4 suite[43]from the difference Patterson synthesis and by direct methods as implemented in SHELX[44]. Both contained a single heavy atom site. Phases, calculated using MLPHARE, were enhanced by solvent flattening4[5] using a solvent content of 50 %. The resulting high quality density map was easily interpretable and the initial model was built using QUANTA (Molecular Simulations) for all but four residues of the construct, ignoring the His-tag. The model was completed with REFMAC (resolution 20-1.9 Å) using a bulk solvent correction, to an R-factor of 23.3 % (R_{Free} 29.7 % - for 5 % of the data). There are 221 residues in the recombinant protein: the first twenty comprise the His-Tag. The final model contains all but two of the 201 residues of the real protein: residues 125-126 are disordered and lie in a flexible surface loop. Only one residue, His0, of the His-tag has clear density and an ordered conformation. In addition there are 187 water molecules, which were selected using ARP[46]during the course of refinement. The main statistics of the refined model are shown in Table 2.

Analytical ultracentrifugation.

Experiments were carried out in an Optima XL-A ultracentrifuge (Beckman-Coultier, CA, USA) using scanning UV optics. During the experiments, the recombinant E2NT was in 10mM TrisHCl pH 8.0, 5mM DTT, 0.2 mM EDTA, 300 mM NaCl.

Data were obtained at rotor speeds of 12,000 and 16,000 rpm, and the time to equilibrium was 10-12 hours. All runs were carried out at 293K, and all radial scans were at a wavelength of 280 nm. Dissociation constants were obtained by nonlinear regression using the Beckman ultracentrifuge software.

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Table 1

X-ray data and phasing statistics

Data set	Native	UAc	AuCN
Space Group	$P3_121$	$P3_121$	$P3_121$
a ,b (Å)	54.68	54.49	54.58
c (Å)	155.73	155.66	156.50
Resolution (Å)	30-1.9	20-2.7	20 - 2.7
Temperature, K	120	120	120
Wavelength (Å)	0.86	0.86	0.86
Unique reflections	21751	7873	7937
Completeness (%) (outer shell)	98.8 (89.3)	99.8 (96.1)	99.7 (93.8)
R-merge (outer shell)	0.058 (0.339)	0.073 (0.271)	0.061 (0.268)
Phasing Power: (centric / acentric)		1.55 / 2.07	0.95 / 1.40
FOM: MIRAS		0.59	
FOM: DM 20-2.7 Å (2.7 - 1.9 Å)		0.88 (0.61)	
DM: Mean phase change (20-2.7 Å)		32 °	
R-factor (FreeR)	0.223 (0.295)		

Table 2

Refinement and model correlation

Resolution		1.9 – 10.0 Å
Number of protein atoms		1622
Number of solvent sites		211
Number of reflections used in refinement		20637
Number of reflections used for Rfree calculation	1111	
R-factor ‡		0.232
Rfree ‡		0.305
Average atomic B-factor*, Å^2	protein atoms	38.0
	water molecules	48.5
R.m.s. deviations from ideal geometry (Å). Targets in parentheses		
	bond distance	0.013 (0.020)
	angle distance	0.026 (0.040)
	chiral volume	0.142 (0.200)

‡Crystallographic R-factor, $R_{(free)} = \sum ||F_o| - |F_c|| / \sum |F_o|$.

Table 3

```
CRYST    54.680   54.680  155.730  90.00  90.00 120.00 P3121
SCALE1       0.01829   0.01056   0.00000         0.00000
SCALE2       0.00000   0.02112   0.00000         0.00000
SCALE3       0.00000   0.00000   0.00642         0.00000
ATOM      1  N   HIS A   0       5.469 -26.512  52.262  1.00 61.92
ATOM      2  CA  HIS A   0       6.434 -25.669  51.568  1.00 61.84
ATOM      3  C   HIS A   0       6.263 -25.743  50.051  1.00 53.91
ATOM      4  O   HIS A   0       6.089 -24.713  49.607  1.00 69.59
ATOM      5  CB  HIS A   0       7.837 -26.127  51.965  1.00 54.18
ATOM      6  CG  HIS A   0       7.848 -26.468  53.431  0.00 99.00
ATOM      7  ND1 HIS A   0       7.914 -25.533  54.412  0.00 99.00
ATOM      8  CD2 HIS A   0       7.732 -27.728  54.027  0.00 99.00
ATOM      9  CE1 HIS A   0       7.828 -26.215  55.570  0.00 99.00
ATOM     10  NE2 HIS A   0       7.723 -27.531  55.370  0.00 99.00
ATOM     11  N   MET A   1       6.663 -26.896  49.478  1.00 56.24
ATOM     12  CA  MET A   1       6.435 -27.076  48.053  1.00 56.42
ATOM     13  C   MET A   1       5.209 -26.282  47.619  1.00 56.07
ATOM     14  O   MET A   1       5.293 -25.299  46.911  1.00 56.51
ATOM     15  CB  MET A   1       6.216 -28.565  47.788  1.00 60.46
ATOM     16  CG  MET A   1       6.856 -29.020  46.477  0.00 99.00
ATOM     17  SD  MET A   1       7.244 -30.775  46.483  0.00 99.00
ATOM     18  CE  MET A   1       7.499 -30.975  44.711  0.00 99.00
ATOM     19  N   GLU A   2       4.035 -26.755  48.064  1.00 54.92
ATOM     20  CA  GLU A   2       2.803 -26.044  47.744  1.00 53.59
```

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ATOM     16  CG  MET A   1       6.856 -29.020  46.477  0.00 99.00
ATOM     17  SD  MET A   1       7.244 -30.775  46.483  0.00 99.00
ATOM     18  CE  MET A   1       7.499 -30.975  44.711  0.00 99.00
ATOM     19  N   GLU A   2       4.035 -26.755  48.064  1.00 54.92
ATOM     20  CA  GLU A   2       2.803 -26.044  47.744  1.00 53.59
ATOM     21  C   GLU A   2       2.870 -24.570  48.154  1.00 52.81
ATOM     22  O   GLU A   2       2.555 -23.664  47.393  1.00 51.69
ATOM     23  CB  GLU A   2       1.661 -26.740  48.482  1.00 56.88
ATOM     24  CG  GLU A   2       2.090 -28.092  49.054  0.00 99.00
ATOM     25  CD  GLU A   2       1.019 -28.610  49.983  0.00 99.00
ATOM     26  OE1 GLU A   2       0.454 -27.819  50.722  0.00 99.00
ATOM     27  OE2 GLU A   2       0.761 -29.811  49.963  0.00 99.00
ATOM     28  N   THR A   3       3.260 -24.346  49.424  1.00 52.06
ATOM     29  CA  THR A   3       3.300 -22.980  49.940  1.00 51.61
ATOM     30  C   THR A   3       4.161 -22.059  49.070  1.00 50.30
ATOM     31  O   THR A   3       3.731 -21.006  48.617  1.00 49.91
ATOM     32  CB  THR A   3       3.858 -23.023  51.364  1.00 54.31
ATOM     33  OG1 THR A   3       2.975 -23.789  52.187  1.00 56.98
ATOM     34  CG2 THR A   3       3.960 -21.605  51.935  1.00 55.18
ATOM     35  N   LEU A   4       5.372 -22.498  48.717  1.00 50.11
ATOM     36  CA  LEU A   4       6.201 -21.696  47.808  1.00 50.48
ATOM     37  C   LEU A   4       5.553 -21.516  46.444  1.00 50.18
ATOM     38  O   LEU A   4       5.520 -20.410  45.877  1.00 50.73
ATOM     39  CB  LEU A   4       7.603 -22.286  47.626  1.00 52.72
ATOM     40  CG  LEU A   4       8.545 -22.252  48.826  1.00 56.58
ATOM     41  CD1 LEU A   4       9.819 -23.035  48.583  1.00 55.37
ATOM     42  CD2 LEU A   4       8.829 -20.828  49.288  1.00 56.27
ATOM     43  N   CYS A   5       5.028 -22.615  45.885  1.00 49.77
ATOM     44  CA  CYS A   5       4.362 -22.530  44.587  1.00 48.93
ATOM     45  C   CYS A   5       3.218 -21.534  44.589  1.00 48.27
ATOM     46  O   CYS A   5       3.136 -20.698  43.682  1.00 47.03
ATOM     47  CB  CYS A   5       3.865 -23.879  44.075  1.00 49.50
ATOM     48  SG  CYS A   5       5.217 -24.972  43.626  1.00 50.79
ATOM     49  N   GLN A   6       2.356 -21.627  45.610  1.00 46.85
ATOM     50  CA  GLN A   6       1.227 -20.718  45.675  1.00 47.22
ATOM     51  C   GLN A   6       1.666 -19.276  45.865  1.00 46.83
ATOM     52  O   GLN A   6       1.050 -18.382  45.276  1.00 48.60
ATOM     53  CB  GLN A   6       0.272 -21.079  46.817  1.00 50.54
ATOM     54  CG  GLN A   6      -0.681 -22.221  46.515  1.00 55.34
ATOM     55  CD  GLN A   6      -1.144 -22.875  47.806  1.00 59.63
ATOM     56  OE1 GLN A   6      -1.101 -22.222  48.853  1.00 61.52
ATOM     57  NE2 GLN A   6      -1.482 -24.156  47.775  1.00 57.45
ATOM     58  N   ARG A   7       2.628 -19.035  46.757  1.00 46.33
ATOM     59  CA  ARG A   7       3.162 -17.700  46.938  1.00 46.38
ATOM     60  C   ARG A   7       3.780 -17.145  45.650  1.00 44.90
ATOM     61  O   ARG A   7       3.544 -15.986  45.355  1.00 45.29
ATOM     62  CB  ARG A   7       4.267 -17.682  48.013  1.00 50.84
ATOM     63  CG  ARG A   7       3.690 -17.869  49.418  1.00 62.38
ATOM     64  CD  ARG A   7       2.884 -16.616  49.765  1.00 71.41
ATOM     65  NE  ARG A   7       3.786 -15.539  50.171  1.00 78.82
ATOM     66  CZ  ARG A   7       3.406 -14.307  50.474  1.00 83.50
ATOM     67  NH1 ARG A   7       2.122 -13.965  50.423  1.00 85.24
ATOM     68  NH2 ARG A   7       4.316 -13.410  50.841  1.00 85.59
ATOM     69  N   LEU A   8       4.608 -17.918  44.984  1.00 45.22
ATOM     70  CA  LEU A   8       5.212 -17.429  43.728  1.00 45.85
ATOM     71  C   LEU A   8       4.161 -17.110  42.672  1.00 46.67
ATOM     72  O   LEU A   8       4.197 -16.055  42.025  1.00 46.25
ATOM     73  CB  LEU A   8       6.185 -18.477  43.194  1.00 41.52
ATOM     74  CG  LEU A   8       6.979 -18.054  41.944  1.00 44.17
ATOM     75  CD1 LEU A   8       7.941 -16.924  42.283  1.00 44.96
ATOM     76  CD2 LEU A   8       7.723 -19.246  41.373  1.00 44.18
ATOM     77  N   ASN A   9       3.193 -18.014  42.508  1.00 47.73
ATOM     78  CA  ASN A   9       2.065 -17.825  41.610  1.00 48.73
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ATOM	79	C	ASN	A	9	1.351	-16.516	41.925	1.00	48.98
ATOM	80	O	ASN	A	9	1.136	-15.727	40.999	1.00	48.98
ATOM	81	CB	ASN	A	9	1.011	-18.923	41.725	1.00	54.35
ATOM	82	CG	ASN	A	9	1.220	-20.167	40.912	1.00	58.01
ATOM	83	OD1	ASN	A	9	2.281	-20.427	40.356	1.00	60.06
ATOM	84	ND2	ASN	A	9	0.174	-20.991	40.841	1.00	63.02
ATOM	85	N	VAL	A	10	1.047	-16.267	43.206	1.00	48.31
ATOM	86	CA	VAL	A	10	0.388	-15.003	43.528	1.00	48.22
ATOM	87	C	VAL	A	10	1.338	-13.837	43.252	1.00	48.34
ATOM	88	O	VAL	A	10	0.931	-12.816	42.688	1.00	47.81
ATOM	89	CB	VAL	A	10	-0.111	-14.918	44.981	1.00	53.07
ATOM	90	CG1	VAL	A	10	-0.501	-13.487	45.353	1.00	53.77
ATOM	91	CG2	VAL	A	10	-1.328	-15.827	45.176	1.00	54.90
ATOM	92	N	CYS	A	11	2.601	-14.011	43.661	1.00	47.68
ATOM	93	CA	CYS	A	11	3.570	-12.938	43.426	1.00	47.78
ATOM	94	C	CYS	A	11	3.747	-12.615	41.954	1.00	47.29
ATOM	95	O	CYS	A	11	3.632	-11.473	41.499	1.00	47.31
ATOM	96	CB	CYS	A	11	4.893	-13.269	44.144	1.00	48.13
ATOM	97	SG	CYS	A	11	6.077	-11.884	44.082	1.00	44.06
ATOM	98	N	GLN	A	12	3.903	-13.633	41.120	1.00	47.63
ATOM	99	CA	GLN	A	12	4.150	-13.484	39.702	1.00	48.32
ATOM	100	C	GLN	A	12	2.936	-12.946	38.951	1.00	48.82
ATOM	101	O	GLN	A	12	3.103	-12.258	37.946	1.00	48.64
ATOM	102	CB	GLN	A	12	4.657	-14.783	39.092	1.00	45.97
ATOM	103	CG	GLN	A	12	6.018	-15.213	39.590	1.00	45.90
ATOM	104	CD	GLN	A	12	6.659	-16.359	38.862	1.00	46.71
ATOM	105	OE1	GLN	A	12	6.028	-17.320	38.425	1.00	45.33
ATOM	106	NE2	GLN	A	12	7.983	-16.294	38.702	1.00	49.43
ATOM	107	N	ASP	A	13	1.736	-13.199	39.470	1.00	48.93
ATOM	108	CA	ASP	A	13	0.516	-12.691	38.853	1.00	49.49
ATOM	109	C	ASP	A	13	0.413	-11.198	39.085	1.00	49.55
ATOM	110	O	ASP	A	13	0.082	-10.444	38.171	1.00	49.73
ATOM	111	CB	ASP	A	13	-0.732	-13.392	39.411	1.00	52.95
ATOM	112	CG	ASP	A	13	-0.955	-14.680	38.932	0.00	99.00
ATOM	113	OD1	ASP	A	13	-0.110	-15.160	38.175	0.00	99.00
ATOM	114	OD2	ASP	A	13	-2.054	-15.191	39.132	0.00	99.00
ATOM	115	N	LYS	A	14	0.801	-10.735	40.269	1.00	48.95
ATOM	116	CA	LYS	A	14	0.809	-9.313	40.556	1.00	49.25
ATOM	117	C	LYS	A	14	1.794	-8.575	39.658	1.00	49.07
ATOM	118	O	LYS	A	14	1.470	-7.519	39.119	1.00	49.78
ATOM	119	CB	LYS	A	14	1.109	-9.040	42.030	1.00	52.53
ATOM	120	CG	LYS	A	14	-0.070	-8.421	42.768	1.00	62.87
ATOM	121	CD	LYS	A	14	-0.269	-6.975	42.329	1.00	66.42
ATOM	122	CE	LYS	A	14	-1.227	-6.247	43.257	1.00	70.58
ATOM	123	NZ	LYS	A	14	-0.835	-4.824	43.452	1.00	72.01
ATOM	124	N	ILE	A	15	2.984	-9.131	39.468	1.00	48.82
ATOM	125	CA	ILE	A	15	3.992	-8.530	38.595	1.00	49.56
ATOM	126	C	ILE	A	15	3.467	-8.390	37.165	1.00	50.17
ATOM	127	O	ILE	A	15	3.538	-7.324	36.561	1.00	50.19
ATOM	128	CB	ILE	A	15	5.288	-9.359	38.669	1.00	43.08
ATOM	129	CG1	ILE	A	15	5.931	-9.100	40.054	1.00	45.94
ATOM	130	CG2	ILE	A	15	6.286	-8.951	37.597	1.00	47.46
ATOM	131	CD1	ILE	A	15	6.960	-10.120	40.472	1.00	42.94
ATOM	132	N	LEU	A	16	2.880	-9.437	36.623	1.00	51.16
ATOM	133	CA	LEU	A	16	2.272	-9.406	35.291	1.00	52.54
ATOM	134	C	LEU	A	16	1.135	-8.414	35.191	1.00	52.81
ATOM	135	O	LEU	A	16	1.023	-7.678	34.194	1.00	53.37
ATOM	136	CB	LEU	A	16	1.859	-10.810	34.847	1.00	56.20
ATOM	137	CG	LEU	A	16	3.067	-11.696	34.504	1.00	61.93
ATOM	138	CD1	LEU	A	16	2.816	-13.139	34.904	1.00	65.17
ATOM	139	CD2	LEU	A	16	3.456	-11.572	33.041	1.00	62.31
ATOM	140	N	THR	A	17	0.274	-8.336	36.204	1.00	52.95
ATOM	141	CA	THR	A	17	-0.789	-7.332	36.217	1.00	53.67

ATOM	142	C	THR	A	17	-0.232	-5.916	36.173	1.00	54.28
ATOM	143	O	THR	A	17	-0.860	-5.026	35.590	1.00	54.21
ATOM	144	CB	THR	A	17	-1.677	-7.468	37.468	1.00	55.51
ATOM	145	OG1	THR	A	17	-2.321	-8.742	37.469	1.00	54.73
ATOM	146	CG2	THR	A	17	-2.713	-6.355	37.551	1.00	52.35
ATOM	147	N	HIS	A	18	0.879	-5.647	36.878	1.00	53.99
ATOM	148	CA	HIS	A	18	1.495	-4.331	36.754	1.00	54.39
ATOM	149	C	HIS	A	18	1.960	-4.115	35.313	1.00	55.01
ATOM	150	O	HIS	A	18	1.722	-3.036	34.757	1.00	54.91
ATOM	151	CB	HIS	A	18	2.663	-4.168	37.735	1.00	53.19
ATOM	152	CG	HIS	A	18	2.198	-3.867	39.130	1.00	52.86
ATOM	153	ND1	HIS	A	18	1.486	-2.733	39.432	1.00	52.60
ATOM	154	CD2	HIS	A	18	2.362	-4.553	40.296	1.00	52.72
ATOM	155	CE1	HIS	A	18	1.216	-2.720	40.730	1.00	53.99
ATOM	156	NE2	HIS	A	18	1.735	-3.817	41.269	1.00	53.27
ATOM	157	N	TYR	A	19	2.580	-5.122	34.721	1.00	56.14
ATOM	158	CA	TYR	A	19	3.044	-5.034	33.337	1.00	58.17
ATOM	159	C	TYR	A	19	1.890	-4.733	32.380	1.00	58.92
ATOM	160	O	TYR	A	19	1.957	-3.827	31.552	1.00	59.36
ATOM	161	CB	TYR	A	19	3.759	-6.320	32.950	1.00	59.47
ATOM	162	CG	TYR	A	19	5.097	-6.621	33.580	1.00	62.05
ATOM	163	CD1	TYR	A	19	5.983	-5.607	33.934	1.00	63.22
ATOM	164	CD2	TYR	A	19	5.513	-7.934	33.787	1.00	62.96
ATOM	165	CE1	TYR	A	19	7.212	-5.891	34.488	1.00	63.58
ATOM	166	CE2	TYR	A	19	6.745	-8.226	34.345	1.00	63.59
ATOM	167	CZ	TYR	A	19	7.597	-7.199	34.703	1.00	63.46
ATOM	168	OH	TYR	A	19	8.828	-7.470	35.274	1.00	62.56
ATOM	169	N	GLU	A	20	0.779	-5.451	32.499	1.00	59.63
ATOM	170	CA	GLU	A	20	-0.426	-5.196	31.734	1.00	59.76
ATOM	171	C	GLU	A	20	-0.990	-3.804	31.918	1.00	59.59
ATOM	172	O	GLU	A	20	-1.198	-3.103	30.928	1.00	59.90
ATOM	173	CB	GLU	A	20	-1.499	-6.241	32.056	1.00	66.29
ATOM	174	CG	GLU	A	20	-1.176	-7.583	31.409	1.00	73.88
ATOM	175	CD	GLU	A	20	-2.142	-8.678	31.815	1.00	78.60
ATOM	176	OE1	GLU	A	20	-1.749	-9.862	31.692	1.00	82.52
ATOM	177	OE2	GLU	A	20	-3.272	-8.365	32.242	1.00	78.94
ATOM	178	N	ASN	A	21	-1.186	-3.340	33.145	1.00	59.04
ATOM	179	CA	ASN	A	21	-1.784	-2.053	33.404	1.00	57.97
ATOM	180	C	ASN	A	21	-1.002	-0.853	32.918	1.00	57.50
ATOM	181	O	ASN	A	21	-1.637	0.118	32.496	1.00	57.19
ATOM	182	CB	ASN	A	21	-2.149	-1.876	34.875	1.00	61.71
ATOM	183	CG	ASN	A	21	-3.089	-2.964	35.362	1.00	63.07
ATOM	184	OD1	ASN	A	21	-3.691	-3.685	34.563	1.00	60.88
ATOM	185	ND2	ASN	A	21	-3.161	-3.066	36.685	1.00	62.59
ATOM	186	N	ASP	A	22	0.327	-0.826	33.022	1.00	56.38
ATOM	187	CA	ASP	A	22	1.080	0.299	32.480	1.00	54.54
ATOM	188	C	ASP	A	22	0.710	1.630	33.112	1.00	53.00
ATOM	189	O	ASP	A	22	0.632	2.652	32.424	1.00	52.65
ATOM	190	CB	ASP	A	22	0.818	0.369	30.967	1.00	61.62
ATOM	191	CG	ASP	A	22	2.107	0.655	30.214	1.00	65.99
ATOM	192	OD1	ASP	A	22	2.946	1.402	30.765	1.00	64.95
ATOM	193	OD2	ASP	A	22	2.235	0.116	29.099	1.00	69.58
ATOM	194	N	SER	A	23	0.616	1.683	34.440	1.00	50.98
ATOM	195	CA	SER	A	23	0.213	2.879	35.148	1.00	49.25
ATOM	196	C	SER	A	23	1.294	3.960	35.095	1.00	48.02
ATOM	197	O	SER	A	23	2.450	3.746	34.740	1.00	47.57
ATOM	198	CB	SER	A	23	-0.101	2.633	36.640	1.00	46.04
ATOM	199	OG	SER	A	23	0.549	1.424	36.984	1.00	56.16
ATOM	200	N	THR	A	24	0.847	5.152	35.441	1.00	47.42
ATOM	201	CA	THR	A	24	1.724	6.312	35.512	1.00	48.00
ATOM	202	C	THR	A	24	1.731	6.860	36.920	1.00	47.34
ATOM	203	O	THR	A	24	2.328	7.898	37.173	1.00	47.41
ATOM	204	CB	THR	A	24	1.369	7.421	34.505	1.00	50.50

ATOM	205	OG1	THR	A	24	0.042	7.871	34.734	1.00	51.02
ATOM	206	CG2	THR	A	24	1.558	6.901	33.094	1.00	48.60
ATOM	207	N	ASP	A	25	1.124	6.096	37.828	1.00	46.98
ATOM	208	CA	ASP	A	25	1.058	6.453	39.234	1.00	46.50
ATOM	209	C	ASP	A	25	2.193	5.788	40.013	1.00	45.63
ATOM	210	O	ASP	A	25	2.376	4.578	40.042	1.00	44.95
ATOM	211	CB	ASP	A	25	-0.286	6.024	39.847	1.00	53.36
ATOM	212	CG	ASP	A	25	-1.442	6.789	39.202	1.00	62.10
ATOM	213	OD1	ASP	A	25	-1.605	7.997	39.498	1.00	64.72
ATOM	214	OD2	ASP	A	25	-2.185	6.192	38.392	1.00	62.72
ATOM	215	N	LEU	A	26	3.000	6.633	40.614	1.00	45.40
ATOM	216	CA	LEU	A	26	4.167	6.207	41.381	1.00	45.37
ATOM	217	C	LEU	A	26	3.834	5.157	42.418	1.00	45.85
ATOM	218	O	LEU	A	26	4.563	4.170	42.565	1.00	46.38
ATOM	219	CB	LEU	A	26	4.763	7.483	41.982	1.00	44.87
ATOM	220	CG	LEU	A	26	6.056	7.341	42.783	1.00	44.69
ATOM	221	CD1	LEU	A	26	7.128	6.688	41.931	1.00	40.20
ATOM	222	CD2	LEU	A	26	6.529	8.703	43.267	1.00	46.93
ATOM	223	N	ARG	A	27	2.741	5.281	43.178	1.00	45.28
ATOM	224	CA	ARG	A	27	2.266	4.241	44.065	1.00	45.19
ATOM	225	C	ARG	A	27	2.251	2.841	43.483	1.00	44.47
ATOM	226	O	ARG	A	27	2.610	1.886	44.187	1.00	44.56
ATOM	227	CB	ARG	A	27	0.852	4.494	44.607	1.00	51.04
ATOM	228	CG	ARG	A	27	0.713	5.531	45.690	1.00	61.27
ATOM	229	CD	ARG	A	27	-0.715	6.081	45.714	1.00	66.89
ATOM	230	NE	ARG	A	27	-0.927	6.984	46.839	1.00	75.54
ATOM	231	CZ	ARG	A	27	-2.083	7.555	47.170	1.00	79.36
ATOM	232	NH1	ARG	A	27	-3.184	7.331	46.456	1.00	80.70
ATOM	233	NH2	ARG	A	27	-2.152	8.359	48.228	1.00	79.78
ATOM	234	N	ASP	A	28	1.771	2.632	42.255	1.00	43.06
ATOM	235	CA	ASP	A	28	1.785	1.318	41.648	1.00	41.77
ATOM	236	C	ASP	A	28	3.195	0.797	41.385	1.00	41.18
ATOM	237	O	ASP	A	28	3.408	-0.409	41.402	1.00	40.08
ATOM	238	CB	ASP	A	28	1.014	1.325	40.303	1.00	44.91
ATOM	239	CG	ASP	A	28	-0.450	1.655	40.560	1.00	53.31
ATOM	240	OD1	ASP	A	28	-1.014	2.560	39.920	1.00	53.29
ATOM	241	OD2	ASP	A	28	-1.022	0.983	41.446	1.00	52.80
ATOM	242	N	HIS	A	29	4.132	1.700	41.062	1.00	40.87
ATOM	243	CA	HIS	A	29	5.510	1.269	40.787	1.00	40.10
ATOM	244	C	HIS	A	29	6.208	0.795	42.073	1.00	39.08
ATOM	245	O	HIS	A	29	6.987	-0.143	42.045	1.00	38.12
ATOM	246	CB	HIS	A	29	6.246	2.473	40.166	1.00	40.60
ATOM	247	CG	HIS	A	29	5.590	2.806	38.837	1.00	42.13
ATOM	248	ND1	HIS	A	29	5.069	1.810	38.042	1.00	42.28
ATOM	249	CD2	HIS	A	29	5.373	3.980	38.192	1.00	44.10
ATOM	250	CE1	HIS	A	29	4.552	2.348	36.943	1.00	43.73
ATOM	251	NE2	HIS	A	29	4.738	3.656	37.014	1.00	42.95
ATOM	252	N	ILE	A	30	5.896	1.454	43.152	1.00	39.44
ATOM	253	CA	ILE	A	30	6.339	0.990	44.501	1.00	39.95
ATOM	254	C	ILE	A	30	5.899	-0.426	44.746	1.00	40.09
ATOM	255	O	ILE	A	30	6.658	-1.303	45.181	1.00	41.16
ATOM	256	CB	ILE	A	30	5.843	1.991	45.550	1.00	40.65
ATOM	257	CG1	ILE	A	30	6.563	3.321	45.334	1.00	40.86
ATOM	258	CG2	ILE	A	30	6.125	1.537	47.004	1.00	41.39
ATOM	259	CD1	ILE	A	30	6.060	4.498	46.138	1.00	42.24
ATOM	260	N	ASP	A	31	4.631	-0.764	44.485	1.00	41.09
ATOM	261	CA	ASP	A	31	4.082	-2.089	44.758	1.00	40.37
ATOM	262	C	ASP	A	31	4.718	-3.130	43.856	1.00	40.59
ATOM	263	O	ASP	A	31	4.965	-4.277	44.244	1.00	40.70
ATOM	264	CB	ASP	A	31	2.566	-2.080	44.459	1.00	42.53
ATOM	265	CG	ASP	A	31	1.886	-3.379	44.801	1.00	44.66
ATOM	266	OD1	ASP	A	31	1.799	-4.311	43.991	1.00	46.03
ATOM	267	OD2	ASP	A	31	1.495	-3.517	45.987	1.00	53.28

ATOM	268	N	TYR	A	32	4.945	-2.735	42.589	1.00	39.00
ATOM	269	CA	TYR	A	32	5.636	-3.647	41.677	1.00	38.51
ATOM	270	C	TYR	A	32	7.017	-4.030	42.231	1.00	36.55
ATOM	271	O	TYR	A	32	7.359	-5.204	42.252	1.00	36.44
ATOM	272	CB	TYR	A	32	5.765	-2.921	40.324	1.00	39.37
ATOM	273	CG	TYR	A	32	6.750	-3.532	39.369	1.00	42.61
ATOM	274	CD1	TYR	A	32	6.374	-4.668	38.646	1.00	45.04
ATOM	275	CD2	TYR	A	32	8.005	-2.989	39.141	1.00	43.12
ATOM	276	CE1	TYR	A	32	7.245	-5.272	37.758	1.00	46.06
ATOM	277	CE2	TYR	A	32	8.871	-3.576	38.235	1.00	44.10
ATOM	278	CZ	TYR	A	32	8.489	-4.707	37.545	1.00	45.75
ATOM	279	OH	TYR	A	32	9.322	-5.303	36.633	1.00	44.58
ATOM	280	N	TRP	A	33	7.850	-3.064	42.552	1.00	36.14
ATOM	281	CA	TRP	A	33	9.183	-3.384	43.061	1.00	36.59
ATOM	282	C	TRP	A	33	9.144	-4.146	44.391	1.00	36.80
ATOM	283	O	TRP	A	33	10.050	-4.951	44.634	1.00	37.42
ATOM	284	CB	TRP	A	33	10.054	-2.131	43.159	1.00	37.44
ATOM	285	CG	TRP	A	33	10.588	-1.813	41.780	1.00	34.77
ATOM	286	CD1	TRP	A	33	10.244	-0.745	40.979	1.00	35.47
ATOM	287	CD2	TRP	A	33	11.522	-2.605	41.047	1.00	32.86
ATOM	288	NE1	TRP	A	33	10.974	-0.822	39.805	1.00	32.84
ATOM	289	CE2	TRP	A	33	11.735	-1.947	39.799	1.00	35.43
ATOM	290	CE3	TRP	A	33	12.209	-3.792	41.301	1.00	32.38
ATOM	291	CZ2	TRP	A	33	12.595	-2.444	38.832	1.00	35.55
ATOM	292	CZ3	TRP	A	33	13.061	-4.282	40.337	1.00	37.27
ATOM	293	CH2	TRP	A	33	13.245	-3.626	39.108	1.00	38.28
ATOM	294	N	LYS	A	34	8.150	-3.912	45.246	1.00	37.05
ATOM	295	CA	LYS	A	34	7.990	-4.765	46.437	1.00	37.56
ATOM	296	C	LYS	A	34	7.687	-6.205	46.060	1.00	37.90
ATOM	297	O	LYS	A	34	8.220	-7.124	46.684	1.00	37.29
ATOM	298	CB	LYS	A	34	6.860	-4.261	47.345	1.00	36.29
ATOM	299	CG	LYS	A	34	7.111	-2.871	47.891	1.00	41.05
ATOM	300	CD	LYS	A	34	6.095	-2.498	48.945	1.00	47.20
ATOM	301	CE	LYS	A	34	5.764	-1.032	48.964	1.00	49.66
ATOM	302	NZ	LYS	A	34	5.046	-0.625	50.219	1.00	57.26
ATOM	303	N	HIS	A	35	6.853	-6.411	45.025	1.00	37.50
ATOM	304	CA	HIS	A	35	6.670	-7.779	44.525	1.00	36.43
ATOM	305	C	HIS	A	35	7.913	-8.328	43.875	1.00	35.96
ATOM	306	O	HIS	A	35	8.237	-9.523	43.986	1.00	34.61
ATOM	307	CB	HIS	A	35	5.446	-7.901	43.587	1.00	40.23
ATOM	308	CG	HIS	A	35	4.200	-7.883	44.428	1.00	44.09
ATOM	309	ND1	HIS	A	35	3.567	-6.711	44.788	1.00	48.39
ATOM	310	CD2	HIS	A	35	3.539	-8.879	45.058	1.00	48.71
ATOM	311	CE1	HIS	A	35	2.538	-6.985	45.574	1.00	48.93
ATOM	312	NE2	HIS	A	35	2.524	-8.283	45.774	1.00	47.98
ATOM	313	N	MET	A	36	8.665	-7.457	43.180	1.00	35.13
ATOM	314	CA	MET	A	36	9.927	-7.985	42.606	1.00	35.12
ATOM	315	C	MET	A	36	10.836	-8.474	43.753	1.00	35.05
ATOM	316	O	MET	A	36	11.472	-9.504	43.634	1.00	34.78
ATOM	317	CB	MET	A	36	10.584	-6.890	41.772	1.00	36.78
ATOM	318	CG	MET	A	36	9.832	-6.601	40.454	1.00	38.38
ATOM	319	SD	MET	A	36	10.026	-7.870	39.206	1.00	39.79
ATOM	320	CE	MET	A	36	11.681	-7.505	38.605	1.00	43.43
ATOM	321	N	ARG	A	37	10.903	-7.746	44.853	1.00	35.39
ATOM	322	CA	ARG	A	37	11.729	-8.145	46.004	1.00	35.09
ATOM	323	C	ARG	A	37	11.240	-9.438	46.667	1.00	34.61
ATOM	324	O	ARG	A	37	12.028	-10.319	46.996	1.00	33.53
ATOM	325	CB	ARG	A	37	11.555	-7.001	47.018	1.00	34.72
ATOM	326	CG	ARG	A	37	12.370	-7.186	48.305	1.00	34.13
ATOM	327	CD	ARG	A	37	12.132	-5.981	49.197	1.00	34.07
ATOM	328	NE	ARG	A	37	12.665	-6.189	50.551	1.00	35.48
ATOM	329	CZ	ARG	A	37	12.420	-5.313	51.520	1.00	33.64
ATOM	330	NH1	ARG	A	37	11.676	-4.228	51.375	1.00	38.49

ATOM	331	NH2	ARG	A	37	12.948	-5.572	52.719	1.00	32.86
ATOM	332	N	LEU	A	38	9.920	-9.544	46.841	1.00	33.92
ATOM	333	CA	LEU	A	38	9.330	-10.768	47.372	1.00	34.82
ATOM	334	C	LEU	A	38	9.592	-11.985	46.532	1.00	36.08
ATOM	335	O	LEU	A	38	9.879	-13.050	47.066	1.00	35.88
ATOM	336	CB	LEU	A	38	7.806	-10.549	47.542	1.00	37.00
ATOM	337	CG	LEU	A	38	7.048	-11.843	47.862	1.00	39.41
ATOM	338	CD1	LEU	A	38	7.338	-12.303	49.271	1.00	36.17
ATOM	339	CD2	LEU	A	38	5.544	-11.698	47.633	1.00	42.91
ATOM	340	N	GLU	A	39	9.532	-11.873	45.176	1.00	36.01
ATOM	341	CA	GLU	A	39	9.903	-12.982	44.328	1.00	35.41
ATOM	342	C	GLU	A	39	11.310	-13.492	44.650	1.00	35.95
ATOM	343	O	GLU	A	39	11.524	-14.706	44.610	1.00	34.71
ATOM	344	CB	GLU	A	39	9.826	-12.621	42.814	1.00	33.83
ATOM	345	CG	GLU	A	39	9.999	-13.858	41.944	1.00	35.55
ATOM	346	CD	GLU	A	39	10.153	-13.499	40.467	1.00	44.56
ATOM	347	OE1	GLU	A	39	11.229	-12.997	40.106	1.00	42.84
ATOM	348	OE2	GLU	A	39	9.219	-13.700	39.690	1.00	42.80
ATOM	349	N	CYS	A	40	12.280	-12.600	44.916	1.00	35.37
ATOM	350	CA	CYS	A	40	13.616	-13.054	45.262	1.00	35.02
ATOM	351	C	CYS	A	40	13.603	-13.852	46.574	1.00	35.78
ATOM	352	O	CYS	A	40	14.329	-14.842	46.621	1.00	35.14
ATOM	353	CB	CYS	A	40	14.587	-11.879	45.434	1.00	34.19
ATOM	354	SG	CYS	A	40	14.743	-10.845	43.945	1.00	35.07
ATOM	355	N	ALA	A	41	12.796	-13.419	47.540	1.00	36.59
ATOM	356	CA	ALA	A	41	12.772	-14.160	48.820	1.00	38.13
ATOM	357	C	ALA	A	41	12.191	-15.553	48.590	1.00	37.52
ATOM	358	O	ALA	A	41	12.659	-16.527	49.200	1.00	38.32
ATOM	359	CB	ALA	A	41	11.955	-13.380	49.827	1.00	36.08
ATOM	360	N	ILE	A	42	11.221	-15.674	47.663	1.00	37.54
ATOM	361	CA	ILE	A	42	10.629	-16.995	47.397	1.00	36.18
ATOM	362	C	ILE	A	42	11.626	-17.922	46.753	1.00	36.44
ATOM	363	O	ILE	A	42	11.856	-19.069	47.133	1.00	35.31
ATOM	364	CB	ILE	A	42	9.325	-16.907	46.581	1.00	36.30
ATOM	365	CG1	ILE	A	42	8.225	-16.165	47.345	1.00	38.51
ATOM	366	CG2	ILE	A	42	8.865	-18.282	46.108	1.00	38.23
ATOM	367	CD1	ILE	A	42	7.114	-15.700	46.390	1.00	41.57
ATOM	368	N	TYR	A	43	12.321	-17.436	45.707	1.00	35.53
ATOM	369	CA	TYR	A	43	13.341	-18.254	45.060	1.00	36.20
ATOM	370	C	TYR	A	43	14.479	-18.536	46.047	1.00	36.21
ATOM	371	O	TYR	A	43	15.091	-19.597	45.993	1.00	36.69
ATOM	372	CB	TYR	A	43	13.884	-17.474	43.838	1.00	36.61
ATOM	373	CG	TYR	A	43	13.065	-17.637	42.572	1.00	38.55
ATOM	374	CD1	TYR	A	43	12.717	-16.512	41.820	1.00	39.59
ATOM	375	CD2	TYR	A	43	12.644	-18.871	42.116	1.00	39.53
ATOM	376	CE1	TYR	A	43	11.998	-16.626	40.646	1.00	41.22
ATOM	377	CE2	TYR	A	43	11.943	-19.006	40.918	1.00	40.40
ATOM	378	CZ	TYR	A	43	11.604	-17.884	40.210	1.00	40.78
ATOM	379	OH	TYR	A	43	10.847	-17.954	39.081	1.00	41.19
ATOM	380	N	TYR	A	44	14.794	-17.563	46.906	1.00	35.43
ATOM	381	CA	TYR	A	44	15.933	-17.815	47.811	1.00	37.45
ATOM	382	C	TYR	A	44	15.547	-19.008	48.716	1.00	37.65
ATOM	383	O	TYR	A	44	16.329	-19.945	48.876	1.00	38.00
ATOM	384	CB	TYR	A	44	16.205	-16.555	48.635	1.00	38.20
ATOM	385	CG	TYR	A	44	17.445	-16.670	49.503	1.00	40.09
ATOM	386	CD1	TYR	A	44	17.398	-17.286	50.756	1.00	41.30
ATOM	387	CD2	TYR	A	44	18.663	-16.206	49.041	1.00	40.77
ATOM	388	CE1	TYR	A	44	18.569	-17.412	51.492	1.00	42.23
ATOM	389	CE2	TYR	A	44	19.833	-16.312	49.776	1.00	42.80
ATOM	390	CZ	TYR	A	44	19.746	-16.907	51.023	1.00	43.39
ATOM	391	OH	TYR	A	44	20.863	-17.049	51.798	1.00	45.51
ATOM	392	N	LYS	A	45	14.334	-18.982	49.224	1.00	38.11
ATOM	393	CA	LYS	A	45	13.891	-20.078	50.118	1.00	40.98

ATOM	394	C	LYS	A	45	13.832	-21.403	49.387	1.00	41.49
ATOM	395	O	LYS	A	45	14.315	-22.472	49.789	1.00	42.02
ATOM	396	CB	LYS	A	45	12.537	-19.754	50.750	1.00	40.25
ATOM	397	CG	LYS	A	45	11.968	-20.894	51.614	1.00	48.19
ATOM	398	CD	LYS	A	45	12.824	-21.269	52.813	1.00	51.93
ATOM	399	CE	LYS	A	45	12.671	-20.308	53.983	1.00	59.68
ATOM	400	NZ	LYS	A	45	13.979	-20.145	54.698	1.00	61.34
ATOM	401	N	ALA	A	46	13.307	-21.357	48.139	1.00	42.39
ATOM	402	CA	ALA	A	46	13.230	-22.586	47.356	1.00	41.88
ATOM	403	C	ALA	A	46	14.613	-23.167	47.179	1.00	41.96
ATOM	404	O	ALA	A	46	14.828	-24.368	47.347	1.00	42.06
ATOM	405	CB	ALA	A	46	12.561	-22.294	46.004	1.00	45.41
ATOM	406	N	ARG	A	47	15.605	-22.341	46.839	1.00	42.18
ATOM	407	CA	ARG	A	47	16.967	-22.806	46.649	1.00	42.89
ATOM	408	C	ARG	A	47	17.567	-23.364	47.949	1.00	44.97
ATOM	409	O	ARG	A	47	18.270	-24.377	47.899	1.00	44.85
ATOM	410	CB	ARG	A	47	17.873	-21.700	46.134	1.00	39.95
ATOM	411	CG	ARG	A	47	19.278	-22.115	45.751	1.00	44.08
ATOM	412	CD	ARG	A	47	19.323	-23.087	44.564	1.00	51.87
ATOM	413	NE	ARG	A	47	20.701	-23.450	44.306	1.00	57.92
ATOM	414	CZ	ARG	A	47	21.372	-24.042	43.351	1.00	62.27
ATOM	415	NH1	ARG	A	47	20.819	-24.506	42.243	1.00	60.85
ATOM	416	NH2	ARG	A	47	22.696	-24.175	43.516	1.00	66.76
ATOM	417	N	GLU	A	48	17.287	-22.673	49.051	1.00	45.14
ATOM	418	CA	GLU	A	48	17.783	-23.090	50.364	1.00	48.18
ATOM	419	C	GLU	A	48	17.266	-24.500	50.681	1.00	48.66
ATOM	420	O	GLU	A	48	18.009	-25.362	51.122	1.00	49.01
ATOM	421	CB	GLU	A	48	17.202	-22.208	51.472	1.00	50.97
ATOM	422	CG	GLU	A	48	17.987	-21.039	51.955	1.00	59.37
ATOM	423	CD	GLU	A	48	17.911	-20.689	53.432	1.00	58.91
ATOM	424	OE1	GLU	A	48	16.891	-20.144	53.912	1.00	64.65
ATOM	425	OE2	GLU	A	48	18.904	-20.949	54.156	1.00	64.43
ATOM	426	N	MET	A	49	16.000	-24.730	50.361	1.00	49.75
ATOM	427	CA	MET	A	49	15.358	-26.017	50.510	1.00	50.42
ATOM	428	C	MET	A	49	15.738	-27.106	49.543	1.00	50.69
ATOM	429	O	MET	A	49	15.197	-28.218	49.620	1.00	51.52
ATOM	430	CB	MET	A	49	13.840	-25.835	50.513	1.00	53.09
ATOM	431	CG	MET	A	49	13.351	-25.048	51.719	1.00	55.67
ATOM	432	SD	MET	A	49	11.617	-24.613	51.508	1.00	64.13
ATOM	433	CE	MET	A	49	10.922	-24.927	53.123	1.00	64.34
ATOM	434	N	GLY	A	50	16.616	-26.852	48.592	1.00	50.09
ATOM	435	CA	GLY	A	50	17.159	-27.787	47.664	1.00	48.51
ATOM	436	C	GLY	A	50	16.332	-27.949	46.384	1.00	48.34
ATOM	437	O	GLY	A	50	16.603	-28.920	45.679	1.00	47.16
ATOM	438	N	PHE	A	51	15.383	-27.074	46.084	1.00	48.32
ATOM	439	CA	PHE	A	51	14.628	-27.205	44.837	1.00	48.99
ATOM	440	C	PHE	A	51	15.442	-26.616	43.675	1.00	49.10
ATOM	441	O	PHE	A	51	16.187	-25.659	43.884	1.00	48.66
ATOM	442	CB	PHE	A	51	13.266	-26.527	44.904	1.00	54.66
ATOM	443	CG	PHE	A	51	12.370	-27.030	46.005	1.00	62.30
ATOM	444	CD1	PHE	A	51	12.237	-28.382	46.261	1.00	66.64
ATOM	445	CD2	PHE	A	51	11.648	-26.142	46.784	1.00	64.64
ATOM	446	CE1	PHE	A	51	11.418	-28.837	47.281	1.00	67.20
ATOM	447	CE2	PHE	A	51	10.813	-26.584	47.788	1.00	65.80
ATOM	448	CZ	PHE	A	51	10.708	-27.937	48.047	1.00	65.88
ATOM	449	N	LYS	A	52	15.455	-27.331	42.554	1.00	49.49
ATOM	450	CA	LYS	A	52	16.204	-26.877	41.377	1.00	48.93
ATOM	451	C	LYS	A	52	15.254	-26.192	40.393	1.00	47.94
ATOM	452	O	LYS	A	52	15.644	-25.414	39.516	1.00	46.65
ATOM	453	CB	LYS	A	52	16.905	-28.073	40.739	1.00	54.00
ATOM	454	CG	LYS	A	52	17.964	-28.697	41.640	1.00	61.04
ATOM	455	CD	LYS	A	52	18.931	-29.536	40.811	1.00	64.27
ATOM	456	CE	LYS	A	52	19.717	-30.537	41.711	0.00	99.00

ATOM	457	NZ	LYS	A	52	20.300	-31.674	41.001	0.00	99.00
ATOM	458	N	HIS	A	53	13.968	-26.480	40.589	1.00	46.17
ATOM	459	CA	HIS	A	53	12.924	-25.816	39.834	1.00	45.58
ATOM	460	C	HIS	A	53	11.697	-25.685	40.724	1.00	44.64
ATOM	461	O	HIS	A	53	11.566	-26.465	41.649	1.00	44.95
ATOM	462	CB	HIS	A	53	12.568	-26.542	38.531	1.00	44.28
ATOM	463	CG	HIS	A	53	11.635	-27.700	38.758	1.00	46.45
ATOM	464	ND1	HIS	A	53	10.277	-27.525	38.978	1.00	45.21
ATOM	465	CD2	HIS	A	53	11.868	-29.026	38.829	1.00	45.27
ATOM	466	CE1	HIS	A	53	9.709	-28.698	39.163	1.00	45.18
ATOM	467	NE2	HIS	A	53	10.655	-29.629	39.076	1.00	49.44
ATOM	468	N	ILE	A	54	10.895	-24.693	40.468	1.00	43.90
ATOM	469	CA	ILE	A	54	9.598	-24.513	41.100	1.00	44.62
ATOM	470	C	ILE	A	54	8.589	-24.354	39.976	1.00	43.53
ATOM	471	O	ILE	A	54	8.704	-23.454	39.123	1.00	44.50
ATOM	472	CB	ILE	A	54	9.627	-23.258	41.996	1.00	51.01
ATOM	473	CG1	ILE	A	54	8.222	-22.740	42.337	1.00	51.18
ATOM	474	CG2	ILE	A	54	10.420	-22.138	41.313	1.00	54.51
ATOM	475	CD1	ILE	A	54	8.293	-22.022	43.690	1.00	55.08
ATOM	476	N	ASN	A	55	7.679	-25.327	39.853	1.00	42.57
ATOM	477	CA	ASN	A	55	6.719	-25.332	38.748	1.00	41.98
ATOM	478	C	ASN	A	55	7.391	-25.383	37.389	1.00	41.70
ATOM	479	O	ASN	A	55	6.958	-24.848	36.368	1.00	41.10
ATOM	480	CB	ASN	A	55	5.639	-24.266	38.828	1.00	41.18
ATOM	481	CG	ASN	A	55	4.611	-24.596	39.915	1.00	45.37
ATOM	482	OD1	ASN	A	55	4.481	-25.766	40.285	1.00	42.95
ATOM	483	ND2	ASN	A	55	3.908	-23.589	40.393	1.00	49.59
ATOM	484	N	HIS	A	56	8.508	-26.115	37.343	1.00	42.09
ATOM	485	CA	HIS	A	56	9.304	-26.336	36.155	1.00	41.80
ATOM	486	C	HIS	A	56	9.996	-25.085	35.651	1.00	42.37
ATOM	487	O	HIS	A	56	10.579	-25.115	34.573	1.00	41.39
ATOM	488	CB	HIS	A	56	8.509	-27.081	35.059	1.00	38.13
ATOM	489	CG	HIS	A	56	8.140	-28.417	35.639	1.00	39.93
ATOM	490	ND1	HIS	A	56	8.997	-29.476	35.683	1.00	40.64
ATOM	491	CD2	HIS	A	56	7.000	-28.811	36.253	1.00	40.69
ATOM	492	CE1	HIS	A	56	8.401	-30.496	36.292	1.00	46.16
ATOM	493	NE2	HIS	A	56	7.192	-30.108	36.648	1.00	44.07
ATOM	494	N	GLN	A	57	10.115	-24.074	36.492	1.00	42.01
ATOM	495	CA	GLN	A	57	10.867	-22.845	36.209	1.00	43.31
ATOM	496	C	GLN	A	57	12.178	-22.922	37.011	1.00	42.73
ATOM	497	O	GLN	A	57	12.135	-23.367	38.159	1.00	42.65
ATOM	498	CB	GLN	A	57	10.017	-21.730	36.771	1.00	44.03
ATOM	499	CG	GLN	A	57	10.191	-20.286	36.476	1.00	54.62
ATOM	500	CD	GLN	A	57	8.889	-19.530	36.723	1.00	54.38
ATOM	501	OE1	GLN	A	57	8.881	-18.332	36.990	1.00	54.35
ATOM	502	NE2	GLN	A	57	7.774	-20.248	36.641	1.00	57.38
ATOM	503	N	VAL	A	58	13.308	-22.526	36.435	1.00	41.67
ATOM	504	CA	VAL	A	58	14.592	-22.695	37.122	1.00	41.06
ATOM	505	C	VAL	A	58	14.654	-21.870	38.395	1.00	39.90
ATOM	506	O	VAL	A	58	14.141	-20.751	38.425	1.00	40.26
ATOM	507	CB	VAL	A	58	15.766	-22.343	36.168	1.00	41.94
ATOM	508	CG1	VAL	A	58	15.770	-20.860	35.859	1.00	41.59
ATOM	509	CG2	VAL	A	58	17.085	-22.872	36.676	1.00	43.75
ATOM	510	N	VAL	A	59	15.193	-22.451	39.461	1.00	40.08
ATOM	511	CA	VAL	A	59	15.414	-21.673	40.713	1.00	40.24
ATOM	512	C	VAL	A	59	16.878	-21.205	40.635	1.00	39.98
ATOM	513	O	VAL	A	59	17.761	-22.042	40.559	1.00	41.27
ATOM	514	CB	VAL	A	59	15.250	-22.591	41.945	1.00	40.48
ATOM	515	CG1	VAL	A	59	15.437	-21.777	43.243	1.00	44.12
ATOM	516	CG2	VAL	A	59	13.830	-23.161	42.037	1.00	39.62
ATOM	517	N	PRO	A	60	17.121	-19.911	40.686	1.00	40.13
ATOM	518	CA	PRO	A	60	18.466	-19.380	40.576	1.00	40.49
ATOM	519	C	PRO	A	60	19.312	-19.737	41.806	1.00	40.57

ATOM	520	O	PRO	A	60	18.766	-20.039	42.863	1.00	39.38
ATOM	521	CB	PRO	A	60	18.272	-17.874	40.580	1.00	40.12
ATOM	522	CG	PRO	A	60	16.837	-17.576	40.657	1.00	40.26
ATOM	523	CD	PRO	A	60	16.069	-18.866	40.722	1.00	39.33
ATOM	524	N	THR	A	61	20.627	-19.662	41.632	1.00	39.59
ATOM	525	CA	THR	A	61	21.502	-19.731	42.799	1.00	39.51
ATOM	526	C	THR	A	61	21.145	-18.651	43.803	1.00	38.37
ATOM	527	O	THR	A	61	20.503	-17.621	43.545	1.00	37.40
ATOM	528	CB	THR	A	61	23.000	-19.670	42.486	1.00	42.80
ATOM	529	OG1	THR	A	61	23.259	-18.498	41.695	1.00	42.80
ATOM	530	CG2	THR	A	61	23.435	-20.914	41.722	1.00	42.91
ATOM	531	N	LEU	A	62	21.544	-18.931	45.058	1.00	37.77
ATOM	532	CA	LEU	A	62	21.280	-17.966	46.132	1.00	36.91
ATOM	533	C	LEU	A	62	21.841	-16.582	45.847	1.00	36.03
ATOM	534	O	LEU	A	62	21.248	-15.566	46.209	1.00	36.36
ATOM	535	CB	LEU	A	62	21.904	-18.492	47.447	1.00	35.93
ATOM	536	CG	LEU	A	62	21.278	-19.807	47.950	1.00	36.47
ATOM	537	CD1	LEU	A	62	22.090	-20.339	49.139	1.00	44.24
ATOM	538	CD2	LEU	A	62	19.850	-19.557	48.450	1.00	33.58
ATOM	539	N	ALA	A	63	23.053	-16.511	45.336	1.00	36.59
ATOM	540	CA	ALA	A	63	23.729	-15.236	45.091	1.00	36.90
ATOM	541	C	ALA	A	63	22.946	-14.476	44.014	1.00	36.28
ATOM	542	O	ALA	A	63	22.808	-13.263	44.128	1.00	35.61
ATOM	543	CB	ALA	A	63	25.153	-15.402	44.601	1.00	39.35
ATOM	544	N	VAL	A	64	22.430	-15.198	43.013	1.00	35.11
ATOM	545	CA	VAL	A	64	21.587	-14.456	42.054	1.00	35.89
ATOM	546	C	VAL	A	64	20.370	-13.842	42.720	1.00	35.12
ATOM	547	O	VAL	A	64	20.062	-12.664	42.487	1.00	34.59
ATOM	548	CB	VAL	A	64	21.180	-15.331	40.855	1.00	37.44
ATOM	549	CG1	VAL	A	64	20.071	-14.660	40.053	1.00	40.96
ATOM	550	CG2	VAL	A	64	22.390	-15.680	40.014	1.00	36.95
ATOM	551	N	SER	A	65	19.616	-14.592	43.540	1.00	35.09
ATOM	552	CA	SER	A	65	18.477	-14.039	44.238	1.00	34.42
ATOM	553	C	SER	A	65	18.854	-12.961	45.225	1.00	34.48
ATOM	554	O	SER	A	65	18.110	-11.986	45.326	1.00	34.19
ATOM	555	CB	SER	A	65	17.583	-15.074	44.940	1.00	34.49
ATOM	556	OG	SER	A	65	17.165	-16.015	43.951	1.00	35.80
ATOM	557	N	LYS	A	66	19.977	-13.079	45.922	1.00	34.79
ATOM	558	CA	LYS	A	66	20.365	-11.976	46.828	1.00	35.44
ATOM	559	C	LYS	A	66	20.611	-10.670	46.044	1.00	35.50
ATOM	560	O	LYS	A	66	20.219	-9.590	46.478	1.00	35.28
ATOM	561	CB	LYS	A	66	21.709	-12.362	47.478	1.00	36.28
ATOM	562	CG	LYS	A	66	21.492	-13.207	48.738	1.00	43.87
ATOM	563	CD	LYS	A	66	22.772	-13.202	49.570	1.00	52.29
ATOM	564	CE	LYS	A	66	23.722	-14.338	49.256	1.00	56.53
ATOM	565	NZ	LYS	A	66	24.326	-14.857	50.541	1.00	60.41
ATOM	566	N	ASN	A	67	21.345	-10.788	44.956	1.00	35.53
ATOM	567	CA	ASN	A	67	21.679	-9.615	44.136	1.00	35.43
ATOM	568	C	ASN	A	67	20.452	-8.955	43.544	1.00	34.46
ATOM	569	O	ASN	A	67	20.370	-7.741	43.518	1.00	33.85
ATOM	570	CB	ASN	A	67	22.657	-10.003	43.019	1.00	39.24
ATOM	571	CG	ASN	A	67	22.999	-8.797	42.163	1.00	49.34
ATOM	572	OD1	ASN	A	67	22.646	-8.711	40.977	1.00	55.32
ATOM	573	ND2	ASN	A	67	23.611	-7.794	42.784	1.00	51.11
ATOM	574	N	LYS	A	68	19.505	-9.746	43.007	1.00	34.69
ATOM	575	CA	LYS	A	68	18.245	-9.160	42.532	1.00	33.90
ATOM	576	C	LYS	A	68	17.421	-8.525	43.620	1.00	33.51
ATOM	577	O	LYS	A	68	16.726	-7.530	43.412	1.00	32.16
ATOM	578	CB	LYS	A	68	17.439	-10.259	41.811	1.00	35.44
ATOM	579	CG	LYS	A	68	18.132	-10.664	40.503	1.00	38.74
ATOM	580	CD	LYS	A	68	17.352	-11.710	39.729	1.00	44.24
ATOM	581	CE	LYS	A	68	15.976	-11.178	39.345	1.00	46.97
ATOM	582	NZ	LYS	A	68	15.414	-12.058	38.260	1.00	51.68

ATOM	583	N	ALA	A	69	17.395	-9.098	44.856	1.00	33.48
ATOM	584	CA	ALA	A	69	16.654	-8.440	45.924	1.00	33.17
ATOM	585	C	ALA	A	69	17.299	-7.103	46.282	1.00	31.99
ATOM	586	O	ALA	A	69	16.620	-6.105	46.498	1.00	31.80
ATOM	587	CB	ALA	A	69	16.642	-9.315	47.213	1.00	31.02
ATOM	588	N	LEU	A	70	18.627	-7.019	46.312	1.00	32.54
ATOM	589	CA	LEU	A	70	19.278	-5.715	46.511	1.00	32.22
ATOM	590	C	LEU	A	70	18.830	-4.668	45.471	1.00	32.04
ATOM	591	O	LEU	A	70	18.604	-3.504	45.815	1.00	32.18
ATOM	592	CB	LEU	A	70	20.800	-5.876	46.425	1.00	35.34
ATOM	593	CG	LEU	A	70	21.431	-6.582	47.652	1.00	41.35
ATOM	594	CD1	LEU	A	70	22.952	-6.614	47.488	1.00	47.21
ATOM	595	CD2	LEU	A	70	21.124	-5.797	48.927	1.00	42.20
ATOM	596	N	GLN	A	71	18.732	-5.068	44.222	1.00	32.28
ATOM	597	CA	GLN	A	71	18.336	-4.184	43.118	1.00	32.66
ATOM	598	C	GLN	A	71	16.888	-3.744	43.319	1.00	33.12
ATOM	599	O	GLN	A	71	16.599	-2.548	43.262	1.00	34.13
ATOM	600	CB	GLN	A	71	18.506	-4.847	41.767	1.00	32.48
ATOM	601	CG	GLN	A	71	19.933	-5.100	41.321	1.00	36.30
ATOM	602	CD	GLN	A	71	20.143	-5.912	40.083	1.00	36.39
ATOM	603	OE1	GLN	A	71	21.103	-5.642	39.339	1.00	42.50
ATOM	604	NE2	GLN	A	71	19.349	-6.917	39.755	1.00	33.68
ATOM	605	N	ALA	A	72	16.008	-4.697	43.668	1.00	32.97
ATOM	606	CA	ALA	A	72	14.624	-4.358	43.963	1.00	32.73
ATOM	607	C	ALA	A	72	14.529	-3.414	45.129	1.00	33.36
ATOM	608	O	ALA	A	72	13.741	-2.468	45.153	1.00	33.02
ATOM	609	CB	ALA	A	72	13.751	-5.597	44.164	1.00	31.63
ATOM	610	N	ILE	A	73	15.314	-3.700	46.205	1.00	32.96
ATOM	611	CA	ILE	A	73	15.341	-2.754	47.321	1.00	32.98
ATOM	612	C	ILE	A	73	15.756	-1.358	46.932	1.00	33.05
ATOM	613	O	ILE	A	73	15.173	-0.371	47.407	1.00	31.52
ATOM	614	CB	ILE	A	73	16.262	-3.309	48.450	1.00	32.37
ATOM	615	CG1	ILE	A	73	15.549	-4.497	49.099	1.00	34.48
ATOM	616	CG2	ILE	A	73	16.564	-2.217	49.479	1.00	36.05
ATOM	617	CD1	ILE	A	73	16.442	-5.452	49.895	1.00	36.56
ATOM	618	N	GLU	A	74	16.821	-1.221	46.107	1.00	33.20
ATOM	619	CA	GLU	A	74	17.249	0.135	45.770	1.00	34.02
ATOM	620	C	GLU	A	74	16.127	0.888	45.042	1.00	33.88
ATOM	621	O	GLU	A	74	15.924	2.077	45.333	1.00	33.58
ATOM	622	CB	GLU	A	74	18.483	0.128	44.849	1.00	42.88
ATOM	623	CG	GLU	A	74	19.730	-0.391	45.551	1.00	50.60
ATOM	624	CD	GLU	A	74	20.121	0.534	46.697	1.00	55.46
ATOM	625	OE1	GLU	A	74	19.809	0.219	47.869	1.00	54.43
ATOM	626	OE2	GLU	A	74	20.627	1.630	46.386	1.00	51.96
ATOM	627	N	LEU	A	75	15.444	0.203	44.142	1.00	34.25
ATOM	628	CA	LEU	A	75	14.353	0.814	43.393	1.00	34.85
ATOM	629	C	LEU	A	75	13.181	1.091	44.339	1.00	35.22
ATOM	630	O	LEU	A	75	12.683	2.215	44.292	1.00	35.32
ATOM	631	CB	LEU	A	75	13.895	-0.038	42.211	1.00	33.68
ATOM	632	CG	LEU	A	75	14.632	0.175	40.849	1.00	40.28
ATOM	633	CD1	LEU	A	75	14.246	1.524	40.263	1.00	38.74
ATOM	634	CD2	LEU	A	75	16.134	0.148	41.044	1.00	41.33
ATOM	635	N	GLN	A	76	12.769	0.098	45.129	1.00	35.20
ATOM	636	CA	GLN	A	76	11.711	0.401	46.107	1.00	34.63
ATOM	637	C	GLN	A	76	12.023	1.622	46.951	1.00	34.20
ATOM	638	O	GLN	A	76	11.197	2.539	47.032	1.00	33.10
ATOM	639	CB	GLN	A	76	11.439	-0.800	47.043	1.00	37.30
ATOM	640	CG	GLN	A	76	10.346	-0.570	48.086	1.00	36.76
ATOM	641	CD	GLN	A	76	10.511	-1.541	49.275	1.00	38.06
ATOM	642	OE1	GLN	A	76	11.019	-2.647	49.179	1.00	36.12
ATOM	643	NE2	GLN	A	76	10.136	-1.178	50.481	1.00	39.68
ATOM	644	N	LEU	A	77	13.195	1.702	47.596	1.00	34.42
ATOM	645	CA	LEU	A	77	13.533	2.857	48.402	1.00	34.29

ATOM	646	C	LEU	A	77	13.506	4.183	47.638	1.00	34.87
ATOM	647	O	LEU	A	77	13.070	5.221	48.149	1.00	32.77
ATOM	648	CB	LEU	A	77	14.906	2.756	49.079	1.00	31.33
ATOM	649	CG	LEU	A	77	14.976	1.566	50.093	1.00	33.32
ATOM	650	CD1	LEU	A	77	16.417	1.466	50.566	1.00	35.24
ATOM	651	CD2	LEU	A	77	14.094	1.902	51.303	1.00	32.76
ATOM	652	N	THR	A	78	14.094	4.162	46.440	1.00	35.43
ATOM	653	CA	THR	A	78	14.147	5.391	45.644	1.00	35.16
ATOM	654	C	THR	A	78	12.754	5.938	45.407	1.00	34.62
ATOM	655	O	THR	A	78	12.561	7.128	45.655	1.00	35.48
ATOM	656	CB	THR	A	78	14.869	5.117	44.306	1.00	33.75
ATOM	657	OG1	THR	A	78	16.212	4.853	44.644	1.00	36.55
ATOM	658	CG2	THR	A	78	14.710	6.309	43.359	1.00	35.96
ATOM	659	N	LEU	A	79	11.867	5.059	44.971	1.00	35.23
ATOM	660	CA	LEU	A	79	10.492	5.458	44.646	1.00	35.59
ATOM	661	C	LEU	A	79	9.738	5.941	45.879	1.00	36.24
ATOM	662	O	LEU	A	79	8.923	6.848	45.814	1.00	34.44
ATOM	663	CB	LEU	A	79	9.744	4.326	43.961	1.00	37.56
ATOM	664	CG	LEU	A	79	10.302	3.825	42.611	1.00	40.81
ATOM	665	CD1	LEU	A	79	9.415	2.708	42.066	1.00	36.86
ATOM	666	CD2	LEU	A	79	10.404	4.981	41.632	1.00	44.33
ATOM	667	N	GLU	A	80	10.058	5.284	47.023	1.00	35.96
ATOM	668	CA	GLU	A	80	9.487	5.773	48.285	1.00	35.25
ATOM	669	C	GLU	A	80	10.002	7.132	48.672	1.00	35.81
ATOM	670	O	GLU	A	80	9.241	7.941	49.182	1.00	36.57
ATOM	671	CB	GLU	A	80	9.805	4.764	49.414	1.00	33.47
ATOM	672	CG	GLU	A	80	8.923	3.555	49.368	1.00	36.03
ATOM	673	CD	GLU	A	80	9.390	2.431	50.293	1.00	39.80
ATOM	674	OE1	GLU	A	80	10.528	2.453	50.789	1.00	38.34
ATOM	675	OE2	GLU	A	80	8.587	1.482	50.397	1.00	40.54
ATOM	676	N	THR	A	81	11.266	7.474	48.443	1.00	35.85
ATOM	677	CA	THR	A	81	11.759	8.819	48.714	1.00	37.65
ATOM	678	C	THR	A	81	11.074	9.798	47.742	1.00	39.27
ATOM	679	O	THR	A	81	10.711	10.894	48.159	1.00	38.93
ATOM	680	CB	THR	A	81	13.277	8.895	48.523	1.00	38.88
ATOM	681	OG1	THR	A	81	13.854	8.188	49.626	1.00	41.45
ATOM	682	CG2	THR	A	81	13.827	10.315	48.511	1.00	37.76
ATOM	683	N	ILE	A	82	10.887	9.360	46.500	1.00	39.69
ATOM	684	CA	ILE	A	82	10.176	10.260	45.568	1.00	41.32
ATOM	685	C	ILE	A	82	8.727	10.458	45.979	1.00	42.17
ATOM	686	O	ILE	A	82	8.195	11.566	45.910	1.00	42.11
ATOM	687	CB	ILE	A	82	10.199	9.735	44.134	1.00	38.27
ATOM	688	CG1	ILE	A	82	11.619	9.500	43.651	1.00	39.22
ATOM	689	CG2	ILE	A	82	9.462	10.697	43.194	1.00	37.66
ATOM	690	CD1	ILE	A	82	12.489	10.717	43.731	1.00	43.59
ATOM	691	N	TYR	A	83	8.097	9.376	46.426	1.00	43.95
ATOM	692	CA	TYR	A	83	6.726	9.469	46.924	1.00	45.07
ATOM	693	C	TYR	A	83	6.597	10.496	48.038	1.00	45.84
ATOM	694	O	TYR	A	83	5.613	11.234	48.097	1.00	44.82
ATOM	695	CB	TYR	A	83	6.229	8.097	47.364	1.00	47.55
ATOM	696	CG	TYR	A	83	4.745	8.146	47.683	1.00	52.04
ATOM	697	CD1	TYR	A	83	3.826	8.070	46.643	1.00	53.71
ATOM	698	CD2	TYR	A	83	4.292	8.292	48.987	1.00	53.75
ATOM	699	CE1	TYR	A	83	2.469	8.119	46.899	1.00	55.59
ATOM	700	CE2	TYR	A	83	2.932	8.343	49.245	1.00	55.42
ATOM	701	CZ	TYR	A	83	2.036	8.252	48.199	1.00	56.63
ATOM	702	OH	TYR	A	83	0.691	8.313	48.454	1.00	58.49
ATOM	703	N	ASN	A	84	7.594	10.600	48.932	1.00	45.54
ATOM	704	CA	ASN	A	84	7.519	11.621	49.959	1.00	46.22
ATOM	705	C	ASN	A	84	7.965	12.989	49.446	1.00	45.99
ATOM	706	O	ASN	A	84	7.812	13.930	50.226	1.00	46.80
ATOM	707	CB	ASN	A	84	8.199	11.252	51.257	1.00	45.97
ATOM	708	CG	ASN	A	84	7.995	9.970	52.011	1.00	42.27

ATOM	709	OD1	ASN	A	84	6.960	9.292	51.955	1.00	48.67
ATOM	710	ND2	ASN	A	84	9.032	9.528	52.753	1.00	40.72
ATOM	711	N	SER	A	85	8.351	13.244	48.201	1.00	44.95
ATOM	712	CA	SER	A	85	8.830	14.568	47.823	1.00	43.57
ATOM	713	C	SER	A	85	7.800	15.337	46.988	1.00	43.08
ATOM	714	O	SER	A	85	6.747	14.845	46.627	1.00	41.05
ATOM	715	CB	SER	A	85	10.108	14.456	46.969	1.00	43.41
ATOM	716	OG	SER	A	85	9.782	14.024	45.656	1.00	38.06
ATOM	717	N	GLN	A	86	8.199	16.543	46.586	1.00	43.58
ATOM	718	CA	GLN	A	86	7.377	17.394	45.725	1.00	44.93
ATOM	719	C	GLN	A	86	7.185	16.853	44.331	1.00	45.37
ATOM	720	O	GLN	A	86	6.311	17.326	43.581	1.00	45.62
ATOM	721	CB	GLN	A	86	8.100	18.761	45.588	1.00	52.00
ATOM	722	CG	GLN	A	86	9.448	18.557	44.909	1.00	58.47
ATOM	723	CD	GLN	A	86	10.263	19.798	44.692	1.00	64.18
ATOM	724	OE1	GLN	A	86	11.330	19.934	45.303	1.00	70.12
ATOM	725	NE2	GLN	A	86	9.786	20.668	43.810	1.00	65.51
ATOM	726	N	TYR	A	87	8.002	15.875	43.915	1.00	45.13
ATOM	727	CA	TYR	A	87	7.886	15.277	42.601	1.00	44.09
ATOM	728	C	TYR	A	87	6.898	14.125	42.585	1.00	44.50
ATOM	729	O	TYR	A	87	6.682	13.536	41.536	1.00	43.83
ATOM	730	CB	TYR	A	87	9.231	14.748	42.072	1.00	42.80
ATOM	731	CG	TYR	A	87	10.318	15.782	42.226	1.00	41.15
ATOM	732	CD1	TYR	A	87	11.376	15.539	43.084	1.00	41.11
ATOM	733	CD2	TYR	A	87	10.272	17.010	41.567	1.00	39.57
ATOM	734	CE1	TYR	A	87	12.344	16.496	43.319	1.00	41.24
ATOM	735	CE2	TYR	A	87	11.243	17.967	41.779	1.00	39.89
ATOM	736	CZ	TYR	A	87	12.295	17.693	42.614	1.00	40.85
ATOM	737	OH	TYR	A	87	13.302	18.594	42.842	1.00	41.44
ATOM	738	N	SER	A	88	6.318	13.805	43.743	1.00	45.60
ATOM	739	CA	SER	A	88	5.478	12.626	43.844	1.00	46.49
ATOM	740	C	SER	A	88	4.368	12.534	42.814	1.00	47.16
ATOM	741	O	SER	A	88	4.080	11.467	42.270	1.00	46.71
ATOM	742	CB	SER	A	88	4.816	12.633	45.245	1.00	48.13
ATOM	743	OG	SER	A	88	4.092	11.417	45.346	1.00	51.98
ATOM	744	N	ASN	A	89	3.667	13.642	42.565	1.00	48.16
ATOM	745	CA	ASN	A	89	2.563	13.593	41.604	1.00	49.94
ATOM	746	C	ASN	A	89	2.888	13.746	40.138	1.00	50.05
ATOM	747	O	ASN	A	89	1.922	13.898	39.362	1.00	49.81
ATOM	748	CB	ASN	A	89	1.500	14.616	42.040	1.00	57.17
ATOM	749	CG	ASN	A	89	1.003	14.286	43.439	1.00	62.53
ATOM	750	OD1	ASN	A	89	0.752	15.195	44.234	1.00	67.35
ATOM	751	ND2	ASN	A	89	0.884	12.995	43.737	1.00	64.39
ATOM	752	N	GLU	A	90	4.149	13.696	39.690	1.00	49.64
ATOM	753	CA	GLU	A	90	4.384	13.669	38.238	1.00	49.09
ATOM	754	C	GLU	A	90	3.952	12.346	37.610	1.00	48.60
ATOM	755	O	GLU	A	90	3.715	11.386	38.327	1.00	47.76
ATOM	756	CB	GLU	A	90	5.891	13.782	37.891	1.00	47.16
ATOM	757	CG	GLU	A	90	6.546	14.906	38.632	1.00	42.61
ATOM	758	CD	GLU	A	90	7.981	15.219	38.359	1.00	44.84
ATOM	759	OE1	GLU	A	90	8.767	14.356	37.961	1.00	46.86
ATOM	760	OE2	GLU	A	90	8.343	16.400	38.592	1.00	45.57
ATOM	761	N	LYS	A	91	3.961	12.276	36.269	1.00	47.66
ATOM	762	CA	LYS	A	91	3.798	10.985	35.595	1.00	47.27
ATOM	763	C	LYS	A	91	5.099	10.180	35.749	1.00	46.58
ATOM	764	O	LYS	A	91	6.181	10.745	35.610	1.00	45.68
ATOM	765	CB	LYS	A	91	3.615	11.124	34.076	1.00	48.52
ATOM	766	CG	LYS	A	91	2.234	10.887	33.509	1.00	55.86
ATOM	767	CD	LYS	A	91	2.206	11.249	32.017	1.00	56.83
ATOM	768	CE	LYS	A	91	2.934	10.173	31.214	1.00	56.89
ATOM	769	NZ	LYS	A	91	3.771	10.752	30.132	1.00	54.96
ATOM	770	N	TRP	A	92	4.971	8.888	36.019	1.00	46.05
ATOM	771	CA	TRP	A	92	6.082	7.961	36.101	1.00	45.89

ATOM	772	C	TRP	A	92	5.702	6.699	35.343	1.00	46.10
ATOM	773	O	TRP	A	92	4.701	6.079	35.668	1.00	46.31
ATOM	774	CB	TRP	A	92	6.454	7.556	37.550	1.00	42.18
ATOM	775	CG	TRP	A	92	6.876	8.733	38.372	1.00	37.28
ATOM	776	CD1	TRP	A	92	6.025	9.494	39.126	1.00	35.98
ATOM	777	CD2	TRP	A	92	8.170	9.326	38.526	1.00	35.45
ATOM	778	NE1	TRP	A	92	6.703	10.512	39.704	1.00	37.68
ATOM	779	CE2	TRP	A	92	8.031	10.426	39.359	1.00	34.31
ATOM	780	CE3	TRP	A	92	9.436	9.034	38.009	1.00	35.29
ATOM	781	CZ2	TRP	A	92	9.085	11.251	39.784	1.00	37.71
ATOM	782	CZ3	TRP	A	92	10.489	9.844	38.391	1.00	34.81
ATOM	783	CH2	TRP	A	92	10.320	10.920	39.272	1.00	37.49
ATOM	784	N	THR	A	93	6.468	6.302	34.333	1.00	46.29
ATOM	785	CA	THR	A	93	6.122	5.105	33.583	1.00	47.56
ATOM	786	C	THR	A	93	6.901	3.910	34.110	1.00	48.41
ATOM	787	O	THR	A	93	7.846	4.126	34.862	1.00	48.37
ATOM	788	CB	THR	A	93	6.370	5.242	32.077	1.00	46.70
ATOM	789	OG1	THR	A	93	7.740	4.928	31.792	1.00	44.41
ATOM	790	CG2	THR	A	93	6.037	6.666	31.629	1.00	44.27
ATOM	791	N	LEU	A	94	6.507	2.716	33.705	1.00	48.40
ATOM	792	CA	LEU	A	94	7.213	1.494	34.076	1.00	48.72
ATOM	793	C	LEU	A	94	8.647	1.507	33.559	1.00	48.08
ATOM	794	O	LEU	A	94	9.587	1.053	34.225	1.00	47.67
ATOM	795	CB	LEU	A	94	6.462	0.294	33.479	1.00	56.38
ATOM	796	CG	LEU	A	94	6.488	-1.036	34.232	1.00	61.49
ATOM	797	CD1	LEU	A	94	6.452	-0.872	35.741	1.00	61.80
ATOM	798	CD2	LEU	A	94	5.310	-1.900	33.781	1.00	62.20
ATOM	799	N	GLN	A	95	8.818	2.022	32.332	1.00	45.95
ATOM	800	CA	GLN	A	95	10.175	2.149	31.805	1.00	43.86
ATOM	801	C	GLN	A	95	10.956	3.201	32.555	1.00	41.09
ATOM	802	O	GLN	A	95	12.138	2.966	32.803	1.00	42.10
ATOM	803	CB	GLN	A	95	10.226	2.431	30.291	1.00	47.51
ATOM	804	CG	GLN	A	95	10.933	1.311	29.532	1.00	55.82
ATOM	805	CD	GLN	A	95	12.441	1.369	29.531	1.00	58.57
ATOM	806	OE1	GLN	A	95	13.085	2.191	28.850	1.00	63.35
ATOM	807	NE2	GLN	A	95	13.089	0.470	30.270	1.00	53.71
ATOM	808	N	ASP	A	96	10.358	4.296	32.984	1.00	39.88
ATOM	809	CA	ASP	A	96	11.048	5.272	33.814	1.00	39.85
ATOM	810	C	ASP	A	96	11.651	4.615	35.076	1.00	40.22
ATOM	811	O	ASP	A	96	12.731	5.042	35.499	1.00	39.43
ATOM	812	CB	ASP	A	96	10.115	6.397	34.246	1.00	40.26
ATOM	813	CG	ASP	A	96	9.603	7.287	33.110	1.00	43.09
ATOM	814	OD1	ASP	A	96	10.290	7.391	32.079	1.00	38.82
ATOM	815	OD2	ASP	A	96	8.516	7.883	33.274	1.00	41.58
ATOM	816	N	VAL	A	97	10.956	3.643	35.651	1.00	39.44
ATOM	817	CA	VAL	A	97	11.371	3.024	36.913	1.00	38.84
ATOM	818	C	VAL	A	97	11.979	1.641	36.744	1.00	38.61
ATOM	819	O	VAL	A	97	12.059	0.843	37.707	1.00	38.87
ATOM	820	CB	VAL	A	97	10.186	2.955	37.903	1.00	40.58
ATOM	821	CG1	VAL	A	97	9.561	4.325	38.123	1.00	37.24
ATOM	822	CG2	VAL	A	97	9.122	1.929	37.569	1.00	39.40
ATOM	823	N	SER	A	98	12.431	1.314	35.539	1.00	37.55
ATOM	824	CA	SER	A	98	12.956	0.014	35.183	1.00	36.27
ATOM	825	C	SER	A	98	14.408	-0.046	35.652	1.00	36.46
ATOM	826	O	SER	A	98	15.028	1.015	35.744	1.00	36.95
ATOM	827	CB	SER	A	98	12.915	-0.142	33.637	1.00	41.66
ATOM	828	OG	SER	A	98	13.869	0.716	32.996	1.00	41.12
ATOM	829	N	LEU	A	99	14.941	-1.247	35.831	1.00	36.38
ATOM	830	CA	LEU	A	99	16.345	-1.378	36.203	1.00	36.81
ATOM	831	C	LEU	A	99	17.251	-0.939	35.042	1.00	36.83
ATOM	832	O	LEU	A	99	18.297	-0.341	35.258	1.00	36.14
ATOM	833	CB	LEU	A	99	16.636	-2.829	36.589	1.00	42.12
ATOM	834	CG	LEU	A	99	18.056	-3.111	37.080	1.00	45.46

ATOM	835	CD1	LEU	A	99	18.330	-2.481	38.442	1.00	43.84
ATOM	836	CD2	LEU	A	99	18.341	-4.606	37.072	1.00	45.55
ATOM	837	N	GLU	A	100	16.797	-1.199	33.818	1.00	36.41
ATOM	838	CA	GLU	A	100	17.488	-0.765	32.611	1.00	37.21
ATOM	839	C	GLU	A	100	17.790	0.722	32.622	1.00	36.02
ATOM	840	O	GLU	A	100	18.972	1.068	32.470	1.00	37.81
ATOM	841	CB	GLU	A	100	16.690	-1.126	31.340	1.00	40.11
ATOM	842	CG	GLU	A	100	17.528	-0.836	30.096	1.00	49.41
ATOM	843	CD	GLU	A	100	16.866	-1.247	28.790	1.00	56.89
ATOM	844	OE1	GLU	A	100	15.724	-1.755	28.761	1.00	57.99
ATOM	845	OE2	GLU	A	100	17.534	-1.025	27.753	1.00	62.25
ATOM	846	N	VAL	A	101	16.808	1.580	32.792	1.00	35.41
ATOM	847	CA	VAL	A	101	17.044	3.010	32.973	1.00	34.54
ATOM	848	C	VAL	A	101	17.897	3.329	34.185	1.00	34.62
ATOM	849	O	VAL	A	101	18.899	4.082	34.151	1.00	33.43
ATOM	850	CB	VAL	A	101	15.666	3.714	33.047	1.00	36.71
ATOM	851	CG1	VAL	A	101	15.797	5.167	33.459	1.00	34.93
ATOM	852	CG2	VAL	A	101	15.013	3.600	31.651	1.00	37.61
ATOM	853	N	TYR	A	102	17.555	2.678	35.314	1.00	33.28
ATOM	854	CA	TYR	A	102	18.202	3.008	36.583	1.00	33.58
ATOM	855	C	TYR	A	102	19.711	2.817	36.484	1.00	33.46
ATOM	856	O	TYR	A	102	20.424	3.624	37.071	1.00	33.95
ATOM	857	CB	TYR	A	102	17.653	2.091	37.691	1.00	34.23
ATOM	858	CG	TYR	A	102	17.996	2.494	39.103	1.00	36.50
ATOM	859	CD1	TYR	A	102	17.325	3.559	39.676	1.00	36.36
ATOM	860	CD2	TYR	A	102	18.961	1.811	39.855	1.00	36.63
ATOM	861	CE1	TYR	A	102	17.582	3.949	40.979	1.00	37.25
ATOM	862	CE2	TYR	A	102	19.237	2.202	41.162	1.00	37.64
ATOM	863	CZ	TYR	A	102	18.537	3.253	41.707	1.00	36.95
ATOM	864	OH	TYR	A	102	18.795	3.693	42.966	1.00	36.81
ATOM	865	N	LEU	A	103	20.170	1.800	35.766	1.00	32.90
ATOM	866	CA	LEU	A	103	21.575	1.513	35.625	1.00	34.69
ATOM	867	C	LEU	A	103	22.225	2.188	34.422	1.00	35.97
ATOM	868	O	LEU	A	103	23.434	2.037	34.247	1.00	37.11
ATOM	869	CB	LEU	A	103	21.811	0.003	35.568	1.00	34.47
ATOM	870	CG	LEU	A	103	21.363	-0.757	36.853	1.00	39.98
ATOM	871	CD1	LEU	A	103	21.588	-2.261	36.702	1.00	40.37
ATOM	872	CD2	LEU	A	103	22.104	-0.231	38.073	1.00	40.86
ATOM	873	N	THR	A	104	21.460	2.913	33.614	1.00	35.72
ATOM	874	CA	THR	A	104	22.115	3.606	32.468	1.00	34.87
ATOM	875	C	THR	A	104	22.792	4.825	33.060	1.00	35.15
ATOM	876	O	THR	A	104	22.206	5.345	34.004	1.00	35.03
ATOM	877	CB	THR	A	104	21.074	4.013	31.409	1.00	36.04
ATOM	878	OG1	THR	A	104	20.507	2.790	30.928	1.00	34.78
ATOM	879	CG2	THR	A	104	21.709	4.722	30.211	1.00	36.74
ATOM	880	N	ALA	A	105	23.907	5.292	32.541	1.00	35.32
ATOM	881	CA	ALA	A	105	24.595	6.446	33.150	1.00	36.34
ATOM	882	C	ALA	A	105	23.662	7.647	33.117	1.00	36.12
ATOM	883	O	ALA	A	105	23.031	7.852	32.074	1.00	35.49
ATOM	884	CB	ALA	A	105	25.840	6.710	32.281	1.00	36.09
ATOM	885	N	PRO	A	106	23.556	8.404	34.195	1.00	35.90
ATOM	886	CA	PRO	A	106	24.273	8.154	35.428	1.00	36.06
ATOM	887	C	PRO	A	106	23.617	7.057	36.275	1.00	35.41
ATOM	888	O	PRO	A	106	22.426	7.141	36.602	1.00	34.13
ATOM	889	CB	PRO	A	106	24.167	9.484	36.175	1.00	36.61
ATOM	890	CG	PRO	A	106	22.880	10.077	35.695	1.00	36.41
ATOM	891	CD	PRO	A	106	22.862	9.725	34.223	1.00	36.94
ATOM	892	N	THR	A	107	24.407	6.045	36.646	1.00	35.50
ATOM	893	CA	THR	A	107	23.833	4.857	37.287	1.00	34.62
ATOM	894	C	THR	A	107	23.256	5.142	38.651	1.00	34.93
ATOM	895	O	THR	A	107	23.639	6.108	39.324	1.00	34.98
ATOM	896	CB	THR	A	107	24.820	3.666	37.301	1.00	39.51
ATOM	897	OG1	THR	A	107	24.114	2.516	37.812	1.00	36.86

ATOM	898	CG2	THR	A	107	26.016	3.957	38.203	1.00 39.22
ATOM	899	N	GLY	A	108	22.272	4.352	39.091	1.00 35.80
ATOM	900	CA	GLY	A	108	21.709	4.504	40.436	1.00 35.25
ATOM	901	C	GLY	A	108	20.719	5.660	40.527	1.00 35.77
ATOM	902	O	GLY	A	108	20.469	6.140	41.646	1.00 35.22
ATOM	903	N	CYS	A	109	20.099	6.080	39.427	1.00 34.86
ATOM	904	CA	CYS	A	109	19.226	7.257	39.416	1.00 35.48
ATOM	905	C	CYS	A	109	17.997	6.934	38.551	1.00 35.39
ATOM	906	O	CYS	A	109	18.179	6.397	37.449	1.00 36.31
ATOM	907	CB	CYS	A	109	19.987	8.395	38.610	1.00 35.03
ATOM	908	SG	CYS	A	109	21.181	9.249	39.651	1.00 42.26
ATOM	909	N	ILE	A	110	16.785	7.158	39.035	1.00 34.76
ATOM	910	CA	ILE	A	110	15.613	7.181	38.156	1.00 34.74
ATOM	911	C	ILE	A	110	15.774	8.456	37.264	1.00 34.48
ATOM	912	O	ILE	A	110	16.234	9.494	37.723	1.00 32.60
ATOM	913	CB	ILE	A	110	14.315	7.414	38.954	1.00 37.69
ATOM	914	CG1	ILE	A	110	14.117	6.274	39.951	1.00 41.68
ATOM	915	CG2	ILE	A	110	13.100	7.594	38.049	1.00 39.85
ATOM	916	CD1	ILE	A	110	13.770	4.943	39.384	1.00 43.84
ATOM	917	N	LYS	A	111	15.373	8.287	36.013	1.00 34.15
ATOM	918	CA	LYS	A	111	15.522	9.400	35.086	1.00 35.30
ATOM	919	C	LYS	A	111	14.453	9.355	34.002	1.00 35.93
ATOM	920	O	LYS	A	111	13.942	8.285	33.702	1.00 35.35
ATOM	921	CB	LYS	A	111	16.879	9.488	34.449	1.00 39.11
ATOM	922	CG	LYS	A	111	17.713	8.300	34.171	1.00 44.79
ATOM	923	CD	LYS	A	111	19.195	8.574	34.494	1.00 41.27
ATOM	924	CE	LYS	A	111	19.930	7.270	34.207	1.00 41.21
ATOM	925	NZ	LYS	A	111	19.943	6.341	35.377	1.00 36.81
ATOM	926	N	LYS	A	112	14.181	10.569	33.482	1.00 36.64
ATOM	927	CA	LYS	A	112	13.194	10.511	32.410	1.00 37.12
ATOM	928	C	LYS	A	112	13.553	11.477	31.283	1.00 38.56
ATOM	929	O	LYS	A	112	14.382	12.368	31.442	1.00 37.40
ATOM	930	CB	LYS	A	112	11.784	10.464	32.883	1.00 45.17
ATOM	931	CG	LYS	A	112	11.274	11.108	34.092	1.00 43.77
ATOM	932	CD	LYS	A	112	9.855	10.826	34.592	1.00 42.31
ATOM	933	CE	LYS	A	112	9.625	11.830	35.702	1.00 40.92
ATOM	934	NZ	LYS	A	112	8.251	12.207	36.085	1.00 41.42
ATOM	935	N	HIS	A	113	12.734	11.353	30.256	1.00 38.75
ATOM	936	CA	HIS	A	113	12.848	12.198	29.053	1.00 39.66
ATOM	937	C	HIS	A	113	14.221	12.110	28.430	1.00 39.88
ATOM	938	O	HIS	A	113	14.895	13.102	28.197	1.00 40.77
ATOM	939	CB	HIS	A	113	12.341	13.611	29.366	1.00 38.57
ATOM	940	CG	HIS	A	113	11.036	13.636	30.115	1.00 38.81
ATOM	941	ND1	HIS	A	113	9.924	12.958	29.655	1.00 42.21
ATOM	942	CD2	HIS	A	113	10.680	14.172	31.299	1.00 41.13
ATOM	943	CE1	HIS	A	113	8.934	13.113	30.518	1.00 37.50
ATOM	944	NE2	HIS	A	113	9.378	13.838	31.529	1.00 43.65
ATOM	945	N	GLY	A	114	14.678	10.906	28.098	1.00 40.03
ATOM	946	CA	GLY	A	114	15.948	10.634	27.465	1.00 42.07
ATOM	947	C	GLY	A	114	15.982	10.869	25.944	1.00 42.05
ATOM	948	O	GLY	A	114	15.006	10.756	25.196	1.00 43.10
ATOM	949	N	TYR	A	115	17.172	11.210	25.445	1.00 42.78
ATOM	950	CA	TYR	A	115	17.369	11.441	24.019	1.00 42.59
ATOM	951	C	TYR	A	115	18.822	11.155	23.637	1.00 42.83
ATOM	952	O	TYR	A	115	19.673	11.182	24.526	1.00 40.37
ATOM	953	CB	TYR	A	115	17.029	12.863	23.612	1.00 43.99
ATOM	954	CG	TYR	A	115	17.877	13.912	24.298	1.00 45.80
ATOM	955	CD1	TYR	A	115	18.944	14.514	23.648	1.00 47.34
ATOM	956	CD2	TYR	A	115	17.628	14.263	25.614	1.00 47.05
ATOM	957	CE1	TYR	A	115	19.718	15.463	24.291	1.00 47.70
ATOM	958	CE2	TYR	A	115	18.375	15.230	26.260	1.00 47.78
ATOM	959	CZ	TYR	A	115	19.398	15.845	25.579	1.00 48.85
ATOM	960	OH	TYR	A	115	20.194	16.754	26.228	1.00 49.73

ATOM	961	N	THR	A	116	19.071	10.953	22.342	1.00	41.33
ATOM	962	CA	THR	A	116	20.415	10.564	21.938	1.00	42.28
ATOM	963	C	THR	A	116	21.285	11.789	21.697	1.00	42.08
ATOM	964	O	THR	A	116	20.858	12.791	21.136	1.00	42.54
ATOM	965	CB	THR	A	116	20.365	9.722	20.643	1.00	46.87
ATOM	966	OG1	THR	A	116	19.589	8.542	20.949	1.00	49.86
ATOM	967	CG2	THR	A	116	21.753	9.272	20.209	1.00	46.71
ATOM	968	N	VAL	A	117	22.552	11.650	22.045	1.00	40.95
ATOM	969	CA	VAL	A	117	23.575	12.638	21.686	1.00	40.83
ATOM	970	C	VAL	A	117	24.538	11.818	20.830	1.00	41.40
ATOM	971	O	VAL	A	117	24.850	10.689	21.222	1.00	41.22
ATOM	972	CB	VAL	A	117	24.297	13.196	22.928	1.00	39.95
ATOM	973	CG1	VAL	A	117	25.599	13.915	22.569	1.00	41.09
ATOM	974	CG2	VAL	A	117	23.375	14.216	23.617	1.00	38.93
ATOM	975	N	GLU	A	118	24.986	12.396	19.713	1.00	41.76
ATOM	976	CA	GLU	A	118	25.908	11.573	18.905	1.00	42.29
ATOM	977	C	GLU	A	118	27.254	12.265	18.832	1.00	42.60
ATOM	978	O	GLU	A	118	27.288	13.498	18.801	1.00	42.94
ATOM	979	CB	GLU	A	118	25.266	11.262	17.556	1.00	46.34
ATOM	980	CG	GLU	A	118	25.923	11.896	16.365	1.00	53.27
ATOM	981	CD	GLU	A	118	25.542	11.270	15.029	1.00	55.37
ATOM	982	OE1	GLU	A	118	24.442	10.707	14.879	1.00	54.40
ATOM	983	OE2	GLU	A	118	26.425	11.358	14.155	1.00	57.58
ATOM	984	N	VAL	A	119	28.322	11.485	18.947	1.00	41.77
ATOM	985	CA	VAL	A	119	29.661	12.031	18.909	1.00	42.33
ATOM	986	C	VAL	A	119	30.408	11.363	17.735	1.00	43.93
ATOM	987	O	VAL	A	119	30.499	10.136	17.672	1.00	42.59
ATOM	988	CB	VAL	A	119	30.486	11.790	20.187	1.00	42.91
ATOM	989	CG1	VAL	A	119	31.894	12.330	19.963	1.00	40.51
ATOM	990	CG2	VAL	A	119	29.868	12.517	21.398	1.00	38.33
ATOM	991	N	GLN	A	120	30.927	12.212	16.870	1.00	44.65
ATOM	992	CA	GLN	A	120	31.698	11.727	15.723	1.00	47.49
ATOM	993	C	GLN	A	120	33.182	11.912	16.001	1.00	50.11
ATOM	994	O	GLN	A	120	33.676	13.040	16.117	1.00	48.28
ATOM	995	CB	GLN	A	120	31.330	12.541	14.481	1.00	48.85
ATOM	996	CG	GLN	A	120	29.834	12.547	14.248	1.00	52.37
ATOM	997	CD	GLN	A	120	29.456	13.089	12.884	1.00	55.34
ATOM	998	OE1	GLN	A	120	30.319	13.536	12.135	1.00	59.08
ATOM	999	NE2	GLN	A	120	28.164	13.016	12.580	1.00	56.41
ATOM	1000	N	PHE	A	121	33.872	10.771	16.065	1.00	52.87
ATOM	1001	CA	PHE	A	121	35.287	10.824	16.382	1.00	58.51
ATOM	1002	C	PHE	A	121	36.147	11.092	15.162	1.00	62.63
ATOM	1003	O	PHE	A	121	37.367	11.134	15.318	1.00	63.15
ATOM	1004	CB	PHE	A	121	35.764	9.660	17.219	1.00	54.96
ATOM	1005	CG	PHE	A	121	35.110	9.596	18.571	1.00	55.06
ATOM	1006	CD1	PHE	A	121	33.983	8.822	18.763	1.00	54.70
ATOM	1007	CD2	PHE	A	121	35.627	10.295	19.641	1.00	52.63
ATOM	1008	CE1	PHE	A	121	33.389	8.726	20.000	1.00	54.52
ATOM	1009	CE2	PHE	A	121	35.032	10.209	20.885	1.00	53.27
ATOM	1010	CZ	PHE	A	121	33.908	9.438	21.065	1.00	53.03
ATOM	1011	N	ASP	A	122	35.547	11.249	13.988	1.00	66.78
ATOM	1012	CA	ASP	A	122	36.246	11.801	12.847	1.00	72.12
ATOM	1013	C	ASP	A	122	35.414	12.152	11.632	1.00	74.59
ATOM	1014	O	ASP	A	122	35.591	13.228	11.042	1.00	75.06
ATOM	1015	CB	ASP	A	122	37.480	10.970	12.495	1.00	80.67
ATOM	1016	CG	ASP	A	122	38.640	11.910	12.201	1.00	84.98
ATOM	1017	OD1	ASP	A	122	38.366	13.018	11.687	1.00	87.13
ATOM	1018	OD2	ASP	A	122	39.782	11.512	12.508	1.00	89.25
ATOM	1019	N	GLY	A	123	34.511	11.277	11.204	1.00	77.06
ATOM	1020	CA	GLY	A	123	33.653	11.544	10.050	1.00	79.12
ATOM	1021	C	GLY	A	123	32.499	10.546	9.975	1.00	80.59
ATOM	1022	O	GLY	A	123	32.702	9.332	10.039	1.00	80.64
ATOM	1023	N	ASP	A	124	31.278	11.063	9.813	1.00	81.67

ATOM	1024	CA	ASP	A	124	30.122	10.180	9.717	1.00	82.77
ATOM	1025	C	ASP	A	124	30.000	9.574	8.324	1.00	82.74
ATOM	1026	O	ASP	A	124	29.673	9.777	7.400	0.00	99.00
ATOM	1027	CB	ASP	A	124	28.828	10.863	10.141	1.00	87.39
ATOM	1028	CG	ASP	A	124	27.968	9.968	11.019	1.00	91.94
ATOM	1029	OD1	ASP	A	124	28.495	8.933	11.489	1.00	93.18
ATOM	1030	OD2	ASP	A	124	26.779	10.288	11.244	1.00	93.68
ATOM	1031	N	ASN	A	127	34.160	6.401	13.268	1.00	58.22
ATOM	1032	CA	ASN	A	127	33.743	5.964	14.601	1.00	58.81
ATOM	1033	C	ASN	A	127	32.728	6.983	15.144	1.00	58.26
ATOM	1034	O	ASN	A	127	33.132	8.096	15.487	1.00	58.82
ATOM	1035	CB	ASN	A	127	34.919	5.955	15.579	1.00	58.33
ATOM	1036	CG	ASN	A	127	35.959	4.889	15.347	1.00	62.63
ATOM	1037	OD1	ASN	A	127	35.660	3.697	15.490	1.00	64.16
ATOM	1038	ND2	ASN	A	127	37.179	5.307	15.008	1.00	60.87
ATOM	1039	N	THR	A	128	31.462	6.617	15.180	1.00	57.71
ATOM	1040	CA	THR	A	128	30.411	7.522	15.665	1.00	57.23
ATOM	1041	C	THR	A	128	29.652	6.846	16.795	1.00	56.48
ATOM	1042	O	THR	A	128	29.065	5.792	16.534	1.00	57.24
ATOM	1043	CB	THR	A	128	29.452	7.842	14.501	1.00	56.65
ATOM	1044	OG1	THR	A	128	30.208	8.579	13.536	1.00	57.99
ATOM	1045	CG2	THR	A	128	28.244	8.653	14.901	1.00	56.34
ATOM	1046	N	MET	A	129	29.705	7.406	18.002	1.00	54.99
ATOM	1047	CA	MET	A	129	29.082	6.817	19.175	1.00	52.19
ATOM	1048	C	MET	A	129	27.768	7.511	19.533	1.00	50.42
ATOM	1049	O	MET	A	129	27.588	8.705	19.319	1.00	48.93
ATOM	1050	CB	MET	A	129	30.009	6.909	20.391	1.00	58.00
ATOM	1051	CG	MET	A	129	31.164	5.934	20.458	1.00	62.68
ATOM	1052	SD	MET	A	129	30.652	4.263	20.904	1.00	68.26
ATOM	1053	CE	MET	A	129	29.906	4.518	22.510	1.00	68.01
ATOM	1054	N	HIS	A	130	26.859	6.735	20.126	1.00	49.01
ATOM	1055	CA	HIS	A	130	25.554	7.194	20.571	1.00	47.13
ATOM	1056	C	HIS	A	130	25.485	7.057	22.095	1.00	46.21
ATOM	1057	O	HIS	A	130	26.009	6.118	22.678	1.00	45.61
ATOM	1058	CB	HIS	A	130	24.436	6.345	19.956	1.00	53.82
ATOM	1059	CG	HIS	A	130	23.967	6.751	18.602	1.00	62.48
ATOM	1060	ND1	HIS	A	130	24.816	7.119	17.581	1.00	66.97
ATOM	1061	CD2	HIS	A	130	22.711	6.825	18.084	1.00	65.45
ATOM	1062	CE1	HIS	A	130	24.114	7.424	16.505	1.00	67.80
ATOM	1063	NE2	HIS	A	130	22.831	7.252	16.784	1.00	68.13
ATOM	1064	N	TYR	A	131	24.998	8.097	22.775	1.00	43.95
ATOM	1065	CA	TYR	A	131	24.923	8.130	24.227	1.00	42.51
ATOM	1066	C	TYR	A	131	23.536	8.666	24.576	1.00	41.94
ATOM	1067	O	TYR	A	131	22.956	9.497	23.829	1.00	41.77
ATOM	1068	CB	TYR	A	131	25.948	9.151	24.762	1.00	42.89
ATOM	1069	CG	TYR	A	131	27.390	8.830	24.392	1.00	42.97
ATOM	1070	CD1	TYR	A	131	27.910	9.421	23.240	1.00	42.76
ATOM	1071	CD2	TYR	A	131	28.205	7.993	25.131	1.00	43.24
ATOM	1072	CE1	TYR	A	131	29.207	9.187	22.828	1.00	44.91
ATOM	1073	CE2	TYR	A	131	29.502	7.765	24.728	1.00	45.47
ATOM	1074	CZ	TYR	A	131	29.991	8.365	23.587	1.00	46.72
ATOM	1075	OH	TYR	A	131	31.295	8.087	23.222	1.00	49.71
ATOM	1076	N	THR	A	132	22.979	8.297	25.721	1.00	40.16
ATOM	1077	CA	THR	A	132	21.666	8.825	26.098	1.00	37.97
ATOM	1078	C	THR	A	132	21.835	9.967	27.066	1.00	37.49
ATOM	1079	O	THR	A	132	22.535	9.779	28.077	1.00	38.05
ATOM	1080	CB	THR	A	132	20.792	7.731	26.746	1.00	38.81
ATOM	1081	OG1	THR	A	132	20.603	6.712	25.757	1.00	36.51
ATOM	1082	CG2	THR	A	132	19.452	8.267	27.216	1.00	36.18
ATOM	1083	N	ASN	A	133	21.212	11.104	26.792	1.00	35.61
ATOM	1084	CA	ASN	A	133	21.188	12.167	27.803	1.00	36.33
ATOM	1085	C	ASN	A	133	19.749	12.266	28.321	1.00	35.53
ATOM	1086	O	ASN	A	133	18.880	11.616	27.771	1.00	35.34

ATOM	1087	CB	ASN	A	133	21.662	13.500	27.280	1.00	36.82
ATOM	1088	CG	ASN	A	133	22.055	14.518	28.327	1.00	42.70
ATOM	1089	OD1	ASN	A	133	22.192	15.696	27.956	1.00	44.62
ATOM	1090	ND2	ASN	A	133	22.275	14.088	29.562	1.00	37.77
ATOM	1091	N	TRP	A	134	19.546	12.925	29.444	1.00	35.65
ATOM	1092	CA	TRP	A	134	18.238	12.908	30.127	1.00	36.02
ATOM	1093	C	TRP	A	134	17.856	14.318	30.510	1.00	36.37
ATOM	1094	O	TRP	A	134	18.686	15.002	31.095	1.00	37.57
ATOM	1095	CB	TRP	A	134	18.363	12.078	31.423	1.00	34.98
ATOM	1096	CG	TRP	A	134	18.900	10.691	31.221	1.00	35.16
ATOM	1097	CD1	TRP	A	134	20.214	10.320	31.363	1.00	36.78
ATOM	1098	CD2	TRP	A	134	18.190	9.511	30.845	1.00	37.83
ATOM	1099	NE1	TRP	A	134	20.350	8.987	31.103	1.00	33.83
ATOM	1100	CE2	TRP	A	134	19.121	8.458	30.802	1.00	34.86
ATOM	1101	CE3	TRP	A	134	16.836	9.240	30.593	1.00	35.07
ATOM	1102	CZ2	TRP	A	134	18.770	7.136	30.516	1.00	36.92
ATOM	1103	CZ3	TRP	A	134	16.498	7.932	30.308	1.00	39.28
ATOM	1104	CH2	TRP	A	134	17.449	6.905	30.240	1.00	38.59
ATOM	1105	N	THR	A	135	16.634	14.807	30.259	1.00	36.82
ATOM	1106	CA	THR	A	135	16.349	16.149	30.758	1.00	36.51
ATOM	1107	C	THR	A	135	16.094	16.125	32.270	1.00	37.13
ATOM	1108	O	THR	A	135	16.234	17.149	32.927	1.00	35.77
ATOM	1109	CB	THR	A	135	15.214	16.871	30.031	1.00	41.31
ATOM	1110	OG1	THR	A	135	13.979	16.175	30.224	1.00	39.42
ATOM	1111	CG2	THR	A	135	15.461	16.910	28.512	1.00	43.30
ATOM	1112	N	HIS	A	136	15.650	15.007	32.831	1.00	36.50
ATOM	1113	CA	HIS	A	136	15.236	14.974	34.227	1.00	37.55
ATOM	1114	C	HIS	A	136	16.017	13.856	34.948	1.00	36.41
ATOM	1115	O	HIS	A	136	15.783	12.717	34.570	1.00	37.39
ATOM	1116	CB	HIS	A	136	13.731	14.716	34.346	1.00	42.28
ATOM	1117	CG	HIS	A	136	12.843	15.884	34.044	1.00	45.85
ATOM	1118	ND1	HIS	A	136	12.928	16.585	32.850	1.00	44.57
ATOM	1119	CD2	HIS	A	136	11.847	16.467	34.751	1.00	47.41
ATOM	1120	CE1	HIS	A	136	12.039	17.564	32.853	1.00	45.33
ATOM	1121	NE2	HIS	A	136	11.362	17.512	33.987	1.00	49.47
ATOM	1122	N	ILE	A	137	16.941	14.223	35.827	1.00	35.44
ATOM	1123	CA	ILE	A	137	17.696	13.165	36.526	1.00	34.42
ATOM	1124	C	ILE	A	137	17.396	13.291	38.023	1.00	34.06
ATOM	1125	O	ILE	A	137	17.573	14.396	38.537	1.00	34.29
ATOM	1126	CB	ILE	A	137	19.209	13.314	36.268	1.00	33.02
ATOM	1127	CG1	ILE	A	137	19.527	13.053	34.780	1.00	33.98
ATOM	1128	CG2	ILE	A	137	19.995	12.315	37.126	1.00	34.85
ATOM	1129	CD1	ILE	A	137	20.948	13.484	34.427	1.00	35.15
ATOM	1130	N	TYR	A	138	16.902	12.217	38.643	1.00	33.90
ATOM	1131	CA	TYR	A	138	16.497	12.371	40.067	1.00	34.35
ATOM	1132	C	TYR	A	138	17.618	11.920	40.998	1.00	34.35
ATOM	1133	O	TYR	A	138	17.925	10.740	40.954	1.00	35.52
ATOM	1134	CB	TYR	A	138	15.196	11.604	40.319	1.00	35.05
ATOM	1135	CG	TYR	A	138	14.075	12.281	39.524	1.00	37.41
ATOM	1136	CD1	TYR	A	138	13.904	11.924	38.203	1.00	38.75
ATOM	1137	CD2	TYR	A	138	13.272	13.267	40.084	1.00	40.04
ATOM	1138	CE1	TYR	A	138	12.922	12.525	37.431	1.00	39.64
ATOM	1139	CE2	TYR	A	138	12.281	13.870	39.308	1.00	41.81
ATOM	1140	CZ	TYR	A	138	12.128	13.492	37.999	1.00	41.16
ATOM	1141	OH	TYR	A	138	11.171	14.050	37.192	1.00	43.58
ATOM	1142	N	ILE	A	139	18.255	12.823	41.721	1.00	34.48
ATOM	1143	CA	ILE	A	139	19.360	12.458	42.607	1.00	35.01
ATOM	1144	C	ILE	A	139	18.756	12.127	43.996	1.00	34.60
ATOM	1145	O	ILE	A	139	18.312	13.089	44.613	1.00	35.20
ATOM	1146	CB	ILE	A	139	20.353	13.612	42.774	1.00	34.61
ATOM	1147	CG1	ILE	A	139	20.926	14.098	41.421	1.00	38.01
ATOM	1148	CG2	ILE	A	139	21.546	13.200	43.637	1.00	37.55
ATOM	1149	CD1	ILE	A	139	21.487	12.956	40.588	1.00	38.91

ATOM	1150	N	CYS	A	140	18.581	10.861	44.301	1.00 35.26
ATOM	1151	CA	CYS	A	140	17.938	10.511	45.590	1.00 37.11
ATOM	1152	C	CYS	A	140	18.952	10.174	46.664	1.00 37.66
ATOM	1153	O	CYS	A	140	19.865	9.384	46.448	1.00 37.82
ATOM	1154	CB	CYS	A	140	17.078	9.251	45.411	1.00 42.45
ATOM	1155	SG	CYS	A	140	15.483	9.689	44.680	1.00 49.17
ATOM	1156	N	GLU	A	141	18.799	10.796	47.831	1.00 37.14
ATOM	1157	CA	GLU	A	141	19.664	10.484	48.966	1.00 37.88
ATOM	1158	C	GLU	A	141	18.845	9.929	50.125	1.00 36.63
ATOM	1159	O	GLU	A	141	17.678	9.579	49.925	1.00 35.72
ATOM	1160	CB	GLU	A	141	20.509	11.709	49.297	1.00 43.42
ATOM	1161	CG	GLU	A	141	21.392	12.145	48.129	1.00 53.61
ATOM	1162	CD	GLU	A	141	22.122	13.446	48.352	1.00 58.09
ATOM	1163	OE1	GLU	A	141	21.544	14.528	48.139	1.00 57.53
ATOM	1164	OE2	GLU	A	141	23.308	13.339	48.747	1.00 64.14
ATOM	1165	N	GLU	A	142	19.445	9.883	51.315	1.00 36.78
ATOM	1166	CA	GLU	A	142	18.783	9.263	52.479	1.00 36.84
ATOM	1167	C	GLU	A	142	17.515	9.941	52.907	1.00 35.85
ATOM	1168	O	GLU	A	142	16.496	9.267	53.166	1.00 36.59
ATOM	1169	CB	GLU	A	142	19.780	9.360	53.654	1.00 43.10
ATOM	1170	CG	GLU	A	142	21.150	8.763	53.466	1.00 54.03
ATOM	1171	CD	GLU	A	142	22.322	9.696	53.311	1.00 60.55
ATOM	1172	OE1	GLU	A	142	22.260	10.679	52.543	1.00 59.21
ATOM	1173	OE2	GLU	A	142	23.401	9.470	53.924	1.00 64.17
ATOM	1174	N	ALA	A	143	17.477	11.272	52.922	1.00 34.96
ATOM	1175	CA	ALA	A	143	16.241	11.960	53.308	1.00 36.52
ATOM	1176	C	ALA	A	143	15.739	12.999	52.312	1.00 36.98
ATOM	1177	O	ALA	A	143	15.239	14.019	52.787	1.00 38.22
ATOM	1178	CB	ALA	A	143	16.560	12.620	54.652	1.00 34.45
ATOM	1179	N	SER	A	144	16.163	12.881	51.031	1.00 36.01
ATOM	1180	CA	SER	A	144	15.754	13.884	50.048	1.00 35.70
ATOM	1181	C	SER	A	144	15.959	13.477	48.583	1.00 35.68
ATOM	1182	O	SER	A	144	16.665	12.520	48.259	1.00 34.04
ATOM	1183	CB	SER	A	144	16.607	15.158	50.246	1.00 39.92
ATOM	1184	OG	SER	A	144	17.965	14.791	49.965	1.00 46.64
ATOM	1185	N	VAL	A	145	15.361	14.287	47.712	1.00 36.14
ATOM	1186	CA	VAL	A	145	15.576	14.054	46.260	1.00 35.49
ATOM	1187	C	VAL	A	145	15.546	15.410	45.563	1.00 36.78
ATOM	1188	O	VAL	A	145	14.806	16.307	45.979	1.00 34.89
ATOM	1189	CB	VAL	A	145	14.580	13.058	45.707	1.00 36.75
ATOM	1190	CG1	VAL	A	145	13.141	13.446	46.028	1.00 36.76
ATOM	1191	CG2	VAL	A	145	14.730	12.908	44.192	1.00 37.20
ATOM	1192	N	THR	A	146	16.453	15.595	44.600	1.00 37.23
ATOM	1193	CA	THR	A	146	16.434	16.814	43.769	1.00 39.11
ATOM	1194	C	THR	A	146	16.529	16.390	42.297	1.00 39.36
ATOM	1195	O	THR	A	146	17.361	15.521	41.981	1.00 39.50
ATOM	1196	CB	THR	A	146	17.709	17.657	44.040	1.00 43.57
ATOM	1197	OG1	THR	A	146	17.833	17.886	45.432	1.00 49.29
ATOM	1198	CG2	THR	A	146	17.686	18.953	43.244	1.00 46.55
ATOM	1199	N	VAL	A	147	15.699	16.998	41.454	1.00 39.48
ATOM	1200	CA	VAL	A	147	15.774	16.719	40.017	1.00 38.72
ATOM	1201	C	VAL	A	147	16.800	17.682	39.433	1.00 39.04
ATOM	1202	O	VAL	A	147	16.921	18.842	39.851	1.00 38.28
ATOM	1203	CB	VAL	A	147	14.451	16.800	39.268	1.00 40.51
ATOM	1204	CG1	VAL	A	147	13.871	18.209	39.197	1.00 42.34
ATOM	1205	CG2	VAL	A	147	14.532	16.183	37.873	1.00 36.37
ATOM	1206	N	VAL	A	148	17.711	17.103	38.634	1.00 39.16
ATOM	1207	CA	VAL	A	148	18.685	17.909	37.910	1.00 38.86
ATOM	1208	C	VAL	A	148	18.569	17.615	36.406	1.00 38.03
ATOM	1209	O	VAL	A	148	18.093	16.554	35.994	1.00 38.38
ATOM	1210	CB	VAL	A	148	20.117	17.663	38.437	1.00 37.94
ATOM	1211	CG1	VAL	A	148	20.196	17.921	39.948	1.00 37.81
ATOM	1212	CG2	VAL	A	148	20.543	16.227	38.135	1.00 39.08

ATOM	1213	N	GLU	A	149	19.105	18.521	35.575	1.00	37.21
ATOM	1214	CA	GLU	A	149	19.010	18.272	34.118	1.00	37.63
ATOM	1215	C	GLU	A	149	20.309	17.767	33.517	1.00	36.45
ATOM	1216	O	GLU	A	149	21.385	18.214	33.912	1.00	37.57
ATOM	1217	CB	GLU	A	149	18.519	19.530	33.403	1.00	48.95
ATOM	1218	CG	GLU	A	149	19.598	20.527	33.046	1.00	53.64
ATOM	1219	CD	GLU	A	149	19.100	21.544	32.022	1.00	58.00
ATOM	1220	OE1	GLU	A	149	19.440	22.716	32.229	1.00	55.36
ATOM	1221	OE2	GLU	A	149	18.363	21.228	31.067	1.00	61.49
ATOM	1222	N	GLY	A	150	20.200	16.861	32.559	1.00	37.43
ATOM	1223	CA	GLY	A	150	21.399	16.289	31.923	1.00	37.28
ATOM	1224	C	GLY	A	150	21.910	17.392	30.970	1.00	37.55
ATOM	1225	O	GLY	A	150	21.071	18.016	30.338	1.00	37.62
ATOM	1226	N	GLN	A	151	23.181	17.714	31.014	1.00	37.21
ATOM	1227	CA	GLN	A	151	23.713	18.812	30.210	1.00	36.92
ATOM	1228	C	GLN	A	151	24.833	18.247	29.331	1.00	37.46
ATOM	1229	O	GLN	A	151	25.351	17.166	29.610	1.00	35.27
ATOM	1230	CB	GLN	A	151	24.280	19.937	31.078	1.00	37.56
ATOM	1231	CG	GLN	A	151	23.177	20.667	31.852	1.00	43.46
ATOM	1232	CD	GLN	A	151	23.691	21.877	32.581	1.00	48.78
ATOM	1233	OE1	GLN	A	151	23.987	22.896	31.946	1.00	49.56
ATOM	1234	NE2	GLN	A	151	23.820	21.769	33.905	1.00	44.12
ATOM	1235	N	VAL	A	152	25.173	19.028	28.294	1.00	36.05
ATOM	1236	CA	VAL	A	152	26.097	18.488	27.284	1.00	36.80
ATOM	1237	C	VAL	A	152	27.209	19.494	26.986	1.00	37.21
ATOM	1238	O	VAL	A	152	26.949	20.667	26.795	1.00	36.72
ATOM	1239	CB	VAL	A	152	25.385	18.266	25.921	1.00	40.17
ATOM	1240	CG1	VAL	A	152	26.394	17.345	25.148	1.00	37.05
ATOM	1241	CG2	VAL	A	152	24.181	17.350	26.088	1.00	42.64
ATOM	1242	N	ASP	A	153	28.420	19.032	27.005	1.00	37.01
ATOM	1243	CA	ASP	A	153	29.712	19.530	26.819	1.00	37.91
ATOM	1244	C	ASP	A	153	30.452	19.060	25.554	1.00	36.17
ATOM	1245	O	ASP	A	153	30.094	18.059	24.955	1.00	37.68
ATOM	1246	CB	ASP	A	153	30.713	19.123	28.066	1.00	30.79
ATOM	1247	CG	ASP	A	153	30.890	20.514	28.634	1.00	39.47
ATOM	1248	OD1	ASP	A	153	30.469	21.441	27.840	1.00	53.60
ATOM	1249	OD2	ASP	A	153	31.411	20.767	29.695	1.00	41.06
ATOM	1250	N	TYR	A	154	31.550	19.785	25.263	1.00	36.73
ATOM	1251	CA	TYR	A	154	32.497	19.232	24.299	1.00	38.06
ATOM	1252	C	TYR	A	154	33.107	17.950	24.912	1.00	38.77
ATOM	1253	O	TYR	A	154	33.386	16.934	24.276	1.00	38.93
ATOM	1254	CB	TYR	A	154	33.624	20.200	23.920	1.00	38.36
ATOM	1255	CG	TYR	A	154	34.637	19.489	23.038	1.00	38.72
ATOM	1256	CD1	TYR	A	154	34.295	19.193	21.714	1.00	39.88
ATOM	1257	CD2	TYR	A	154	35.875	19.104	23.514	1.00	39.51
ATOM	1258	CE1	TYR	A	154	35.184	18.532	20.873	1.00	39.95
ATOM	1259	CE2	TYR	A	154	36.759	18.454	22.687	1.00	41.22
ATOM	1260	CZ	TYR	A	154	36.412	18.174	21.376	1.00	41.17
ATOM	1261	OH	TYR	A	154	37.332	17.516	20.610	1.00	42.16
ATOM	1262	N	TYR	A	155	33.319	18.027	26.224	1.00	38.13
ATOM	1263	CA	TYR	A	155	33.883	16.968	27.018	1.00	38.84
ATOM	1264	C	TYR	A	155	32.959	15.819	27.350	1.00	37.80
ATOM	1265	O	TYR	A	155	33.530	14.735	27.543	1.00	37.77
ATOM	1266	CB	TYR	A	155	34.500	17.518	28.323	1.00	40.03
ATOM	1267	CG	TYR	A	155	35.364	18.745	28.031	1.00	43.75
ATOM	1268	CD1	TYR	A	155	34.854	20.021	28.230	1.00	44.64
ATOM	1269	CD2	TYR	A	155	36.655	18.604	27.562	1.00	44.86
ATOM	1270	CE1	TYR	A	155	35.628	21.136	27.950	1.00	46.55
ATOM	1271	CE2	TYR	A	155	37.440	19.709	27.271	1.00	46.37
ATOM	1272	CZ	TYR	A	155	36.920	20.963	27.485	1.00	48.04
ATOM	1273	OH	TYR	A	155	37.708	22.064	27.230	1.00	50.62
ATOM	1274	N	GLY	A	156	31.651	16.005	27.491	1.00	36.89
ATOM	1275	CA	GLY	A	156	30.784	14.894	27.833	1.00	36.27

ATOM	1276	C	GLY	A	156	29.374	15.297	28.278	1.00	36.29
ATOM	1277	O	GLY	A	156	28.845	16.351	27.962	1.00	36.73
ATOM	1278	N	LEU	A	157	28.737	14.367	28.989	1.00	35.47
ATOM	1279	CA	LEU	A	157	27.410	14.593	29.547	1.00	36.71
ATOM	1280	C	LEU	A	157	27.570	14.782	31.061	1.00	36.98
ATOM	1281	O	LEU	A	157	28.299	14.009	31.703	1.00	37.91
ATOM	1282	CB	LEU	A	157	26.472	13.404	29.348	1.00	36.06
ATOM	1283	CG	LEU	A	157	26.409	12.902	27.878	1.00	39.11
ATOM	1284	CD1	LEU	A	157	25.362	11.777	27.835	1.00	40.34
ATOM	1285	CD2	LEU	A	157	25.944	14.021	26.948	1.00	37.66
ATOM	1286	N	TYR	A	158	26.860	15.773	31.583	1.00	36.59
ATOM	1287	CA	TYR	A	158	27.043	16.018	33.020	1.00	37.29
ATOM	1288	C	TYR	A	158	25.778	16.579	33.654	1.00	37.06
ATOM	1289	O	TYR	A	158	24.813	16.941	32.968	1.00	36.78
ATOM	1290	CB	TYR	A	158	28.202	17.007	33.172	1.00	37.24
ATOM	1291	CG	TYR	A	158	27.948	18.410	32.664	1.00	38.25
ATOM	1292	CD1	TYR	A	158	27.547	19.427	33.526	1.00	37.59
ATOM	1293	CD2	TYR	A	158	28.158	18.721	31.322	1.00	38.51
ATOM	1294	CE1	TYR	A	158	27.355	20.718	33.056	1.00	38.42
ATOM	1295	CE2	TYR	A	158	27.955	20.009	30.839	1.00	38.37
ATOM	1296	CZ	TYR	A	158	27.573	21.006	31.711	1.00	38.61
ATOM	1297	OH	TYR	A	158	27.359	22.290	31.260	1.00	37.90
ATOM	1298	N	TYR	A	159	25.799	16.661	34.979	1.00	36.65
ATOM	1299	CA	TYR	A	159	24.758	17.394	35.694	1.00	37.45
ATOM	1300	C	TYR	A	159	25.493	18.169	36.801	1.00	37.16
ATOM	1301	O	TYR	A	159	26.659	17.920	37.045	1.00	37.16
ATOM	1302	CB	TYR	A	159	23.638	16.543	36.301	1.00	37.42
ATOM	1303	CG	TYR	A	159	24.161	15.441	37.222	1.00	37.53
ATOM	1304	CD1	TYR	A	159	24.429	14.181	36.732	1.00	39.31
ATOM	1305	CD2	TYR	A	159	24.352	15.689	38.574	1.00	38.15
ATOM	1306	CE1	TYR	A	159	24.902	13.169	37.564	1.00	39.89
ATOM	1307	CE2	TYR	A	159	24.823	14.699	39.407	1.00	38.54
ATOM	1308	CZ	TYR	A	159	25.101	13.454	38.893	1.00	39.58
ATOM	1309	OH	TYR	A	159	25.613	12.488	39.741	1.00	40.63
ATOM	1310	N	VAL	A	160	24.779	19.122	37.356	1.00	36.88
ATOM	1311	CA	VAL	A	160	25.251	19.943	38.452	1.00	38.20
ATOM	1312	C	VAL	A	160	24.277	19.714	39.629	1.00	38.68
ATOM	1313	O	VAL	A	160	23.078	19.922	39.514	1.00	38.89
ATOM	1314	CB	VAL	A	160	25.295	21.439	38.094	1.00	41.01
ATOM	1315	CG1	VAL	A	160	25.815	22.251	39.288	1.00	39.83
ATOM	1316	CG2	VAL	A	160	26.254	21.687	36.916	1.00	36.61
ATOM	1317	N	HIS	A	161	24.818	19.208	40.708	1.00	39.08
ATOM	1318	CA	HIS	A	161	24.018	18.916	41.919	1.00	39.84
ATOM	1319	C	HIS	A	161	24.734	19.569	43.095	1.00	39.51
ATOM	1320	O	HIS	A	161	25.900	19.316	43.322	1.00	38.92
ATOM	1321	CB	HIS	A	161	23.939	17.418	42.140	1.00	37.10
ATOM	1322	CG	HIS	A	161	23.189	16.976	43.377	1.00	36.87
ATOM	1323	ND1	HIS	A	161	21.908	17.363	43.665	1.00	42.27
ATOM	1324	CD2	HIS	A	161	23.571	16.163	44.374	1.00	38.66
ATOM	1325	CE1	HIS	A	161	21.508	16.811	44.805	1.00	34.42
ATOM	1326	NE2	HIS	A	161	22.503	16.079	45.262	1.00	40.76
ATOM	1327	N	GLU	A	162	24.031	20.404	43.832	1.00	41.45
ATOM	1328	CA	GLU	A	162	24.557	21.115	44.998	1.00	43.07
ATOM	1329	C	GLU	A	162	25.795	21.928	44.616	1.00	42.85
ATOM	1330	O	GLU	A	162	26.806	21.828	45.304	1.00	43.43
ATOM	1331	CB	GLU	A	162	24.930	20.138	46.121	1.00	46.97
ATOM	1332	CG	GLU	A	162	23.750	19.235	46.415	1.00	59.55
ATOM	1333	CD	GLU	A	162	23.494	18.891	47.854	1.00	61.68
ATOM	1334	OE1	GLU	A	162	22.551	19.508	48.387	1.00	66.02
ATOM	1335	OE2	GLU	A	162	24.226	18.027	48.364	1.00	65.49
ATOM	1336	N	GLY	A	163	25.786	22.518	43.432	1.00	43.79
ATOM	1337	CA	GLY	A	163	26.930	23.253	42.929	1.00	43.51
ATOM	1338	C	GLY	A	163	28.023	22.409	42.306	1.00	43.73

ATOM	1339	O	GLY	A	163	28.958	23.011	41.746	1.00 43.41
ATOM	1340	N	ILE	A	164	27.986	21.079	42.371	1.00 42.17
ATOM	1341	CA	ILE	A	164	29.078	20.258	41.896	1.00 41.52
ATOM	1342	C	ILE	A	164	28.743	19.687	40.513	1.00 41.11
ATOM	1343	O	ILE	A	164	27.677	19.110	40.314	1.00 40.21
ATOM	1344	CB	ILE	A	164	29.442	19.081	42.820	1.00 41.77
ATOM	1345	CG1	ILE	A	164	29.730	19.597	44.228	1.00 46.60
ATOM	1346	CG2	ILE	A	164	30.651	18.346	42.258	1.00 43.25
ATOM	1347	CD1	ILE	A	164	29.708	18.526	45.303	1.00 50.89
ATOM	1348	N	ARG	A	165	29.613	20.004	39.561	1.00 40.27
ATOM	1349	CA	ARG	A	165	29.428	19.508	38.202	1.00 40.37
ATOM	1350	C	ARG	A	165	29.979	18.082	38.132	1.00 40.18
ATOM	1351	O	ARG	A	165	31.139	17.889	38.436	1.00 40.87
ATOM	1352	CB	ARG	A	165	30.211	20.389	37.205	1.00 43.98
ATOM	1353	CG	ARG	A	165	30.190	19.775	35.799	1.00 48.81
ATOM	1354	CD	ARG	A	165	31.056	20.614	34.844	1.00 50.67
ATOM	1355	NE	ARG	A	165	30.374	21.882	34.644	1.00 54.50
ATOM	1356	CZ	ARG	A	165	30.245	22.592	33.535	1.00 51.25
ATOM	1357	NH1	ARG	A	165	30.788	22.211	32.399	1.00 52.55
ATOM	1358	NH2	ARG	A	165	29.552	23.727	33.612	1.00 46.13
ATOM	1359	N	THR	A	166	29.159	17.127	37.747	1.00 38.84
ATOM	1360	CA	THR	A	166	29.502	15.722	37.710	1.00 37.91
ATOM	1361	C	THR	A	166	29.318	15.152	36.310	1.00 36.66
ATOM	1362	O	THR	A	166	28.167	15.109	35.857	1.00 36.77
ATOM	1363	CB	THR	A	166	28.621	14.911	38.700	1.00 42.71
ATOM	1364	OG1	THR	A	166	28.895	15.399	40.034	1.00 43.09
ATOM	1365	CG2	THR	A	166	28.934	13.427	38.662	1.00 40.93
ATOM	1366	N	TYR	A	167	30.398	14.733	35.667	1.00 36.29
ATOM	1367	CA	TYR	A	167	30.309	14.112	34.342	1.00 36.95
ATOM	1368	C	TYR	A	167	29.970	12.639	34.466	1.00 37.76
ATOM	1369	O	TYR	A	167	30.561	11.961	35.335	1.00 39.69
ATOM	1370	CB	TYR	A	167	31.611	14.231	33.518	1.00 37.91
ATOM	1371	CG	TYR	A	167	31.797	15.617	32.933	1.00 38.45
ATOM	1372	CD1	TYR	A	167	32.311	16.637	33.726	1.00 39.32
ATOM	1373	CD2	TYR	A	167	31.397	15.937	31.646	1.00 39.69
ATOM	1374	CE1	TYR	A	167	32.458	17.919	33.243	1.00 38.98
ATOM	1375	CE2	TYR	A	167	31.535	17.214	31.133	1.00 39.08
ATOM	1376	CZ	TYR	A	167	32.064	18.201	31.946	1.00 40.35
ATOM	1377	OH	TYR	A	167	32.216	19.488	31.494	1.00 39.61
ATOM	1378	N	PHE	A	168	28.924	12.172	33.821	1.00 37.39
ATOM	1379	CA	PHE	A	168	28.547	10.772	33.818	1.00 38.28
ATOM	1380	C	PHE	A	168	28.987	10.058	32.559	1.00 39.29
ATOM	1381	O	PHE	A	168	28.980	8.825	32.494	1.00 38.30
ATOM	1382	CB	PHE	A	168	27.085	10.508	34.167	1.00 38.07
ATOM	1383	CG	PHE	A	168	26.068	11.226	33.320	1.00 34.93
ATOM	1384	CD1	PHE	A	168	25.596	10.661	32.153	1.00 36.11
ATOM	1385	CD2	PHE	A	168	25.609	12.470	33.722	1.00 35.04
ATOM	1386	CE1	PHE	A	168	24.656	11.337	31.364	1.00 34.93
ATOM	1387	CE2	PHE	A	168	24.672	13.140	32.951	1.00 35.38
ATOM	1388	CZ	PHE	A	168	24.215	12.564	31.799	1.00 30.80
ATOM	1389	N	VAL	A	169	29.331	10.849	31.524	1.00 39.59
ATOM	1390	CA	VAL	A	169	30.019	10.310	30.354	1.00 40.03
ATOM	1391	C	VAL	A	169	31.149	11.322	30.039	1.00 41.32
ATOM	1392	O	VAL	A	169	30.904	12.530	30.018	1.00 39.98
ATOM	1393	CB	VAL	A	169	29.136	10.155	29.112	1.00 39.59
ATOM	1394	CG1	VAL	A	169	29.988	9.684	27.917	1.00 41.55
ATOM	1395	CG2	VAL	A	169	28.019	9.107	29.242	1.00 38.14
ATOM	1396	N	GLN	A	170	32.377	10.844	29.870	1.00 41.92
ATOM	1397	CA	GLN	A	170	33.464	11.693	29.396	1.00 42.70
ATOM	1398	C	GLN	A	170	33.833	11.215	27.990	1.00 43.33
ATOM	1399	O	GLN	A	170	34.348	10.097	27.861	1.00 43.22
ATOM	1400	CB	GLN	A	170	34.696	11.627	30.293	1.00 39.48
ATOM	1401	CG	GLN	A	170	34.448	12.220	31.676	1.00 45.31

ATOM	1402	CD	GLN	A	170	35.691	12.212	32.542	1.00	46.68
ATOM	1403	OE1	GLN	A	170	35.649	11.848	33.717	1.00	52.69
ATOM	1404	NE2	GLN	A	170	36.816	12.618	31.998	1.00	47.58
ATOM	1405	N	PHE	A	171	33.678	12.076	26.982	1.00	43.04
ATOM	1406	CA	PHE	A	171	33.884	11.606	25.629	1.00	44.34
ATOM	1407	C	PHE	A	171	35.302	11.186	25.340	1.00	45.84
ATOM	1408	O	PHE	A	171	35.508	10.343	24.446	1.00	45.10
ATOM	1409	CB	PHE	A	171	33.422	12.612	24.597	1.00	39.68
ATOM	1410	CG	PHE	A	171	31.961	12.978	24.639	1.00	38.24
ATOM	1411	CD1	PHE	A	171	31.016	11.986	24.875	1.00	40.47
ATOM	1412	CD2	PHE	A	171	31.530	14.269	24.412	1.00	35.50
ATOM	1413	CE1	PHE	A	171	29.673	12.310	24.905	1.00	37.70
ATOM	1414	CE2	PHE	A	171	30.187	14.604	24.441	1.00	37.98
ATOM	1415	CZ	PHE	A	171	29.248	13.621	24.690	1.00	37.99
ATOM	1416	N	LYS	A	172	36.287	11.662	26.080	1.00	45.69
ATOM	1417	CA	LYS	A	172	37.660	11.223	25.889	1.00	47.54
ATOM	1418	C	LYS	A	172	37.949	9.748	26.138	1.00	48.27
ATOM	1419	O	LYS	A	172	38.884	9.175	25.570	1.00	48.26
ATOM	1420	CB	LYS	A	172	38.594	12.102	26.708	1.00	52.42
ATOM	1421	CG	LYS	A	172	40.022	12.159	26.201	1.00	57.12
ATOM	1422	CD	LYS	A	172	40.904	12.971	27.157	1.00	64.24
ATOM	1423	CE	LYS	A	172	42.362	12.543	27.018	1.00	65.59
ATOM	1424	NZ	LYS	A	172	43.304	13.691	26.949	1.00	65.87
ATOM	1425	N	ASP	A	173	37.154	9.132	27.009	1.00	48.25
ATOM	1426	CA	ASP	A	173	37.212	7.712	27.287	1.00	49.23
ATOM	1427	C	ASP	A	173	36.954	6.925	26.007	1.00	49.36
ATOM	1428	O	ASP	A	173	37.788	6.072	25.701	1.00	49.13
ATOM	1429	CB	ASP	A	173	36.263	7.269	28.394	1.00	46.27
ATOM	1430	CG	ASP	A	173	36.627	7.869	29.740	1.00	50.82
ATOM	1431	OD1	ASP	A	173	35.740	8.056	30.605	1.00	51.86
ATOM	1432	OD2	ASP	A	173	37.817	8.158	29.970	1.00	52.02
ATOM	1433	N	ASP	A	174	35.901	7.144	25.248	1.00	49.89
ATOM	1434	CA	ASP	A	174	35.671	6.430	24.007	1.00	50.79
ATOM	1435	C	ASP	A	174	36.647	6.784	22.897	1.00	52.00
ATOM	1436	O	ASP	A	174	37.085	5.884	22.165	1.00	51.37
ATOM	1437	CB	ASP	A	174	34.231	6.582	23.539	1.00	51.65
ATOM	1438	CG	ASP	A	174	33.276	5.662	24.274	1.00	51.83
ATOM	1439	OD1	ASP	A	174	33.751	4.664	24.847	1.00	48.40
ATOM	1440	OD2	ASP	A	174	32.060	5.942	24.269	1.00	52.72
ATOM	1441	N	ALA	A	175	37.040	8.053	22.808	1.00	52.36
ATOM	1442	CA	ALA	A	175	38.024	8.476	21.821	1.00	53.78
ATOM	1443	C	ALA	A	175	39.362	7.759	21.964	1.00	54.22
ATOM	1444	O	ALA	A	175	39.999	7.417	20.974	1.00	54.32
ATOM	1445	CB	ALA	A	175	38.226	9.986	21.910	1.00	51.67
ATOM	1446	N	GLU	A	176	39.832	7.508	23.186	1.00	55.55
ATOM	1447	CA	GLU	A	176	41.120	6.865	23.409	1.00	56.73
ATOM	1448	C	GLU	A	176	41.015	5.357	23.234	1.00	57.74
ATOM	1449	O	GLU	A	176	42.025	4.646	23.187	1.00	58.14
ATOM	1450	CB	GLU	A	176	41.655	7.170	24.806	1.00	56.85
ATOM	1451	CG	GLU	A	176	41.910	8.632	25.116	1.00	59.30
ATOM	1452	CD	GLU	A	176	42.180	8.743	26.537	0.00	99.00
ATOM	1453	OE1	GLU	A	176	41.740	8.063	27.454	0.00	99.00
ATOM	1454	OE2	GLU	A	176	43.073	9.574	26.687	0.00	99.00
ATOM	1455	N	LYS	A	177	39.790	4.852	23.170	1.00	58.44
ATOM	1456	CA	LYS	A	177	39.555	3.420	23.024	1.00	59.70
ATOM	1457	C	LYS	A	177	39.312	3.069	21.561	1.00	60.20
ATOM	1458	O	LYS	A	177	39.326	1.895	21.198	1.00	60.71
ATOM	1459	CB	LYS	A	177	38.350	3.040	23.887	1.00	63.58
ATOM	1460	CG	LYS	A	177	38.054	1.569	24.029	1.00	67.87
ATOM	1461	CD	LYS	A	177	37.047	1.277	25.140	1.00	70.02
ATOM	1462	CE	LYS	A	177	36.872	-0.235	25.242	1.00	73.46
ATOM	1463	NZ	LYS	A	177	36.221	-0.638	26.517	1.00	75.57
ATOM	1464	N	TYR	A	178	38.908	4.057	20.758	1.00	60.36

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ATOM   1465  CA  TYR A 178      38.551   3.798  19.381  1.00 61.69
ATOM   1466  C   TYR A 178      39.369   4.563  18.361  1.00 62.23
ATOM   1467  O   TYR A 178      39.821   3.923  17.409  1.00 63.37
ATOM   1468  CB  TYR A 178      37.057   3.988  19.100  1.00 61.34
ATOM   1469  CG  TYR A 178      36.139   3.197  20.010  1.00 61.39
ATOM   1470  CD1 TYR A 178      36.249   1.811  20.081  1.00 62.10
ATOM   1471  CD2 TYR A 178      35.189   3.821  20.798  1.00 61.28
ATOM   1472  CE1 TYR A 178      35.440   1.072  20.929  1.00 62.32
ATOM   1473  CE2 TYR A 178      34.378   3.097  21.651  1.00 62.22
ATOM   1474  CZ  TYR A 178      34.505   1.723  21.707  1.00 62.51
ATOM   1475  OH  TYR A 178      33.696   0.989  22.540  1.00 62.15
ATOM   1476  N   SER A 179      39.573   5.858  18.525  1.00 62.95
ATOM   1477  CA  SER A 179      40.159   6.703  17.498  1.00 64.19
ATOM   1478  C   SER A 179      41.662   6.923  17.631  1.00 64.98
ATOM   1479  O   SER A 179      42.279   6.550  18.630  1.00 64.79
ATOM   1480  CB  SER A 179      39.470   8.077  17.505  1.00 65.34
ATOM   1481  OG  SER A 179      39.982   8.923  16.491  1.00 69.64
ATOM   1482  N   LYS A 180      42.254   7.552  16.609  1.00 65.75
ATOM   1483  CA  LYS A 180      43.672   7.876  16.658  1.00 66.93
ATOM   1484  C   LYS A 180      43.886   9.316  17.107  1.00 67.25
ATOM   1485  O   LYS A 180      44.806   9.591  17.887  1.00 67.85
ATOM   1486  CB  LYS A 180      44.431   7.615  15.360  1.00 69.83
ATOM   1487  CG  LYS A 180      45.938   7.673  15.581  1.00 73.65
ATOM   1488  CD  LYS A 180      46.681   8.326  14.427  1.00 76.04
ATOM   1489  CE  LYS A 180      48.016   8.889  14.887  1.00 75.99
ATOM   1490  NZ  LYS A 180      47.829  10.056  15.790  1.00 78.28
ATOM   1491  N   ASN A 181      43.017  10.216  16.652  1.00 66.93
ATOM   1492  CA  ASN A 181      43.126  11.609  17.113  1.00 66.52
ATOM   1493  C   ASN A 181      42.128  11.842  18.240  1.00 65.58
ATOM   1494  O   ASN A 181      41.133  11.131  18.348  1.00 65.86
ATOM   1495  CB  ASN A 181      43.174  12.454  16.113  0.00 99.00
ATOM   1496  CG  ASN A 181      44.528  12.902  15.624  0.00 99.00
ATOM   1497  OD1 ASN A 181      45.545  12.248  15.833  0.00 99.00
ATOM   1498  ND2 ASN A 181      44.525  14.056  14.935  0.00 99.00
ATOM   1499  N   LYS A 182      42.432  12.756  19.155  1.00 65.06
ATOM   1500  CA  LYS A 182      41.483  13.086  20.232  1.00 62.47
ATOM   1501  C   LYS A 182      40.755  14.370  19.855  1.00 60.44
ATOM   1502  O   LYS A 182      40.951  15.405  20.491  1.00 60.89
ATOM   1503  CB  LYS A 182      42.257  13.224  21.544  1.00 68.03
ATOM   1504  CG  LYS A 182      41.462  13.626  22.774  1.00 70.69
ATOM   1505  CD  LYS A 182      42.223  14.606  23.651  1.00 73.12
ATOM   1506  CE  LYS A 182      41.360  15.246  24.718  1.00 73.28
ATOM   1507  NZ  LYS A 182      40.729  16.534  24.325  1.00 74.63
ATOM   1508  N   VAL A 183      40.007  14.401  18.761  1.00 58.04
ATOM   1509  CA  VAL A 183      39.240  15.559  18.324  1.00 55.16
ATOM   1510  C   VAL A 183      37.899  15.073  17.781  1.00 52.42
ATOM   1511  O   VAL A 183      37.902  14.220  16.898  1.00 52.43
ATOM   1512  CB  VAL A 183      39.936  16.462  17.302  1.00 58.84
ATOM   1513  CG1 VAL A 183      38.965  17.219  16.395  1.00 61.12
ATOM   1514  CG2 VAL A 183      40.809  17.504  18.010  1.00 60.87
ATOM   1515  N   TRP A 184      36.785  15.581  18.302  1.00 49.48
ATOM   1516  CA  TRP A 184      35.495  15.042  17.878  1.00 45.59
ATOM   1517  C   TRP A 184      34.490  16.159  17.706  1.00 44.01
ATOM   1518  O   TRP A 184      34.791  17.353  17.913  1.00 42.88
ATOM   1519  CB  TRP A 184      35.049  13.926  18.839  1.00 42.62
ATOM   1520  CG  TRP A 184      35.075  14.460  20.253  1.00 39.47
ATOM   1521  CD1 TRP A 184      34.123  15.236  20.830  1.00 37.50
ATOM   1522  CD2 TRP A 184      36.109  14.271  21.216  1.00 41.84
ATOM   1523  NE1 TRP A 184      34.491  15.541  22.123  1.00 36.00
ATOM   1524  CE2 TRP A 184      35.717  14.963  22.380  1.00 39.37
ATOM   1525  CE3 TRP A 184      37.328  13.587  21.201  1.00 39.30
ATOM   1526  CZ2 TRP A 184      36.504  14.983  23.529  1.00 41.08
ATOM   1527  CZ3 TRP A 184      38.105  13.599  22.341  1.00 41.95
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ATOM	1528	CH2	TRP	A	184	37.692	14.293	23.486	1.00	42.37
ATOM	1529	N	GLU	A	185	33.292	15.809	17.270	1.00	42.34
ATOM	1530	CA	GLU	A	185	32.211	16.770	17.099	1.00	42.70
ATOM	1531	C	GLU	A	185	30.950	16.204	17.765	1.00	43.74
ATOM	1532	O	GLU	A	185	30.589	15.062	17.506	1.00	43.14
ATOM	1533	CB	GLU	A	185	31.903	17.074	15.635	1.00	42.03
ATOM	1534	CG	GLU	A	185	33.023	17.900	14.999	1.00	38.91
ATOM	1535	CD	GLU	A	185	32.851	18.134	13.528	1.00	42.12
ATOM	1536	OE1	GLU	A	185	31.953	17.527	12.910	1.00	40.53
ATOM	1537	OE2	GLU	A	185	33.641	18.955	13.015	1.00	39.53
ATOM	1538	N	VAL	A	186	30.374	17.021	18.653	1.00	43.76
ATOM	1539	CA	VAL	A	186	29.211	16.563	19.400	1.00	43.51
ATOM	1540	C	VAL	A	186	27.943	17.165	18.791	1.00	45.37
ATOM	1541	O	VAL	A	186	27.804	18.379	18.647	1.00	43.51
ATOM	1542	CB	VAL	A	186	29.339	17.008	20.872	1.00	41.67
ATOM	1543	CG1	VAL	A	186	28.159	16.494	21.688	1.00	41.68
ATOM	1544	CG2	VAL	A	186	30.697	16.596	21.452	1.00	34.89
ATOM	1545	N	HIS	A	187	27.012	16.272	18.454	1.00	46.62
ATOM	1546	CA	HIS	A	187	25.679	16.656	18.003	1.00	50.05
ATOM	1547	C	HIS	A	187	24.620	16.257	19.023	1.00	52.23
ATOM	1548	O	HIS	A	187	24.447	15.055	19.262	1.00	52.60
ATOM	1549	CB	HIS	A	187	25.329	15.949	16.672	1.00	51.22
ATOM	1550	CG	HIS	A	187	26.356	16.159	15.600	1.00	53.27
ATOM	1551	ND1	HIS	A	187	26.135	16.916	14.467	1.00	55.72
ATOM	1552	CD2	HIS	A	187	27.633	15.710	15.495	1.00	54.05
ATOM	1553	CE1	HIS	A	187	27.216	16.925	13.713	1.00	49.24
ATOM	1554	NE2	HIS	A	187	28.134	16.205	14.329	1.00	53.78
ATOM	1555	N	ALA	A	188	23.836	17.199	19.524	1.00	54.61
ATOM	1556	CA	ALA	A	188	22.883	16.882	20.591	1.00	57.68
ATOM	1557	C	ALA	A	188	21.502	17.477	20.393	1.00	59.90
ATOM	1558	O	ALA	A	188	20.747	17.673	21.356	1.00	60.86
ATOM	1559	CB	ALA	A	188	23.501	17.291	21.929	1.00	57.50
ATOM	1560	N	GLY	A	189	21.107	17.773	19.155	1.00	61.42
ATOM	1561	CA	GLY	A	189	19.809	18.381	18.867	1.00	62.45
ATOM	1562	C	GLY	A	189	19.862	19.892	18.710	1.00	62.76
ATOM	1563	O	GLY	A	189	18.863	20.613	18.809	1.00	63.40
ATOM	1564	N	GLY	A	190	21.051	20.429	18.448	1.00	62.37
ATOM	1565	CA	GLY	A	190	21.211	21.883	18.338	1.00	60.60
ATOM	1566	C	GLY	A	190	22.551	22.159	17.660	1.00	58.62
ATOM	1567	O	GLY	A	190	23.029	21.274	16.958	1.00	58.39
ATOM	1568	N	GLN	A	191	23.173	23.285	17.983	1.00	56.77
ATOM	1569	CA	GLN	A	191	24.466	23.554	17.336	1.00	54.69
ATOM	1570	C	GLN	A	191	25.462	22.451	17.687	1.00	52.57
ATOM	1571	O	GLN	A	191	25.599	22.082	18.858	1.00	52.69
ATOM	1572	CB	GLN	A	191	24.972	24.927	17.760	1.00	58.35
ATOM	1573	CG	GLN	A	191	26.437	25.200	17.502	1.00	62.97
ATOM	1574	CD	GLN	A	191	26.166	26.948	17.561	0.00	99.00
ATOM	1575	OE1	GLN	A	191	25.459	27.683	16.891	0.00	99.00
ATOM	1576	NE2	GLN	A	191	27.070	27.403	18.451	0.00	99.00
ATOM	1577	N	VAL	A	192	26.162	21.943	16.684	1.00	49.07
ATOM	1578	CA	VAL	A	192	27.264	21.012	16.898	1.00	45.59
ATOM	1579	C	VAL	A	192	28.237	21.647	17.875	1.00	44.47
ATOM	1580	O	VAL	A	192	28.473	22.853	17.803	1.00	45.15
ATOM	1581	CB	VAL	A	192	27.960	20.717	15.544	1.00	42.50
ATOM	1582	CG1	VAL	A	192	29.047	19.665	15.684	1.00	39.90
ATOM	1583	CG2	VAL	A	192	26.874	20.237	14.584	1.00	40.84
ATOM	1584	N	ILE	A	193	28.831	20.882	18.775	1.00	41.81
ATOM	1585	CA	ILE	A	193	29.875	21.406	19.636	1.00	39.71
ATOM	1586	C	ILE	A	193	31.246	21.009	19.127	1.00	40.00
ATOM	1587	O	ILE	A	193	31.569	19.822	19.009	1.00	40.12
ATOM	1588	CB	ILE	A	193	29.715	20.868	21.104	1.00	36.14
ATOM	1589	CG1	ILE	A	193	28.303	21.218	21.573	1.00	38.63
ATOM	1590	CG2	ILE	A	193	30.765	21.585	21.957	1.00	38.85

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ATOM   1591  CD1 ILE A 193      27.916  20.591  22.922  1.00 41.29
ATOM   1592  N   LEU A 194      32.075  22.008  18.852  1.00 39.67
ATOM   1593  CA  LEU A 194      33.436  21.783  18.388  1.00 40.23
ATOM   1594  C   LEU A 194      34.455  21.944  19.486  1.00 40.97
ATOM   1595  O   LEU A 194      34.136  22.489  20.557  1.00 40.07
ATOM   1596  CB  LEU A 194      33.741  22.794  17.252  1.00 38.19
ATOM   1597  CG  LEU A 194      32.736  22.764  16.101  1.00 42.91
ATOM   1598  CD1 LEU A 194      33.203  23.702  14.980  1.00 42.33
ATOM   1599  CD2 LEU A 194      32.593  21.362  15.514  1.00 41.05
ATOM   1600  N   CYS A 195      35.658  21.430  19.269  1.00 41.29
ATOM   1601  CA  CYS A 195      36.711  21.575  20.273  1.00 43.15
ATOM   1602  C   CYS A 195      36.956  23.045  20.562  1.00 45.32
ATOM   1603  O   CYS A 195      37.083  23.872  19.671  1.00 44.47
ATOM   1604  CB  CYS A 195      37.981  20.893  19.785  1.00 44.75
ATOM   1605  SG  CYS A 195      39.358  21.057  20.920  1.00 43.19
ATOM   1606  N   PRO A 196      36.918  23.423  21.847  1.00 46.44
ATOM   1607  CA  PRO A 196      36.978  24.814  22.245  1.00 47.49
ATOM   1608  C   PRO A 196      38.376  25.335  22.514  1.00 48.05
ATOM   1609  O   PRO A 196      38.575  26.531  22.759  1.00 49.91
ATOM   1610  CB  PRO A 196      36.123  24.820  23.515  1.00 48.09
ATOM   1611  CG  PRO A 196      36.293  23.449  24.079  1.00 47.48
ATOM   1612  CD  PRO A 196      36.834  22.513  23.018  1.00 47.09
ATOM   1613  N   THR A 197      39.365  24.477  22.488  1.00 48.20
ATOM   1614  CA  THR A 197      40.753  24.821  22.766  1.00 49.51
ATOM   1615  C   THR A 197      41.610  24.697  21.491  1.00 48.70
ATOM   1616  O   THR A 197      41.132  24.143  20.508  1.00 47.51
ATOM   1617  CB  THR A 197      41.337  23.819  23.789  1.00 54.19
ATOM   1618  OG1 THR A 197      42.063  22.755  23.133  1.00 60.20
ATOM   1619  CG2 THR A 197      40.249  23.146  24.620  1.00 60.00
ATOM   1620  N   SER A 198      42.874  25.104  21.600  1.00 48.43
ATOM   1621  CA  SER A 198      43.755  25.011  20.443  1.00 49.41
ATOM   1622  C   SER A 198      44.106  23.572  20.088  1.00 51.13
ATOM   1623  O   SER A 198      44.340  22.748  20.974  1.00 50.32
ATOM   1624  CB  SER A 198      45.022  25.837  20.600  1.00 41.67
ATOM   1625  OG  SER A 198      44.689  27.176  20.863  1.00 42.21
ATOM   1626  N   VAL A 199      44.135  23.321  18.783  1.00 51.78
ATOM   1627  CA  VAL A 199      44.448  22.018  18.210  1.00 54.21
ATOM   1628  C   VAL A 199      45.846  22.063  17.593  1.00 55.85
ATOM   1629  O   VAL A 199      46.229  23.043  16.958  1.00 55.32
ATOM   1630  CB  VAL A 199      43.415  21.673  17.105  1.00 55.83
ATOM   1631  CG1 VAL A 199      43.848  20.450  16.311  1.00 58.48
ATOM   1632  CG2 VAL A 199      42.081  21.363  17.794  1.00 58.90
ATOM   1633  N   PHE A 200      46.643  21.031  17.823  1.00 57.80
ATOM   1634  CA  PHE A 200      48.033  20.977  17.458  1.00 60.84
ATOM   1635  C   PHE A 200      48.501  19.863  16.538  1.00 63.34
ATOM   1636  O   PHE A 200      47.988  18.771  16.373  1.00 63.71
ATOM   1637  CB  PHE A 200      48.976  20.962  18.695  1.00 56.48
ATOM   1638  CG  PHE A 200      49.009  22.350  19.286  1.00 51.93
ATOM   1639  CD1 PHE A 200      49.867  23.304  18.779  1.00 50.53
ATOM   1640  CD2 PHE A 200      48.118  22.686  20.298  1.00 52.06
ATOM   1641  CE1 PHE A 200      49.844  24.596  19.289  1.00 48.79
ATOM   1642  CE2 PHE A 200      48.104  23.972  20.813  1.00 46.67
ATOM   1643  CZ  PHE A 200      48.952  24.921  20.283  1.00 48.73
ATOM   1644  N   SER A 201      49.612  20.201  15.906  1.00 65.54
ATOM   1645  CA  SER A 201      50.520  19.367  15.151  1.00 67.49
ATOM   1646  C   SER A 201      50.543  17.927  15.652  1.00 68.56
ATOM   1647  O   SER A 201      50.873  17.710  16.841  1.00 69.46
ATOM   1648  CB  SER A 201      51.928  19.984  15.374  1.00 69.06
ATOM   1649  OG  SER A 201      51.799  21.376  15.666  1.00 64.56
ATOM   1650  OT  SER A 201      50.201  17.025  14.856  1.00 71.71
ATOM   1651  OW0 WAT W   1      16.850   8.350  41.749  1.00 33.70
ATOM   1652  OW0 WAT W   2      14.700   3.706  36.739  1.00 34.70
ATOM   1653  OW0 WAT W   3      23.512 -21.581  45.725  1.00 35.04
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ATOM	1654	OW0	WAT	W	4	13.647	-16.192	51.826	1.00	35.32
ATOM	1655	OW0	WAT	W	5	27.151	6.021	35.728	1.00	35.70
ATOM	1656	OW0	WAT	W	6	35.841	19.641	17.028	1.00	36.41
ATOM	1657	OW0	WAT	W	7	12.924	7.105	31.382	1.00	36.46
ATOM	1658	OW0	WAT	W	8	22.396	20.058	35.878	1.00	36.81
ATOM	1659	OW0	WAT	W	9	17.562	-18.568	44.759	1.00	38.24
ATOM	1660	OW0	WAT	W	10	23.931	7.992	29.610	1.00	38.55
ATOM	1661	OW0	WAT	W	11	32.085	22.981	25.237	1.00	38.76
ATOM	1662	OW0	WAT	W	12	18.237	6.493	43.333	1.00	38.96
ATOM	1663	OW0	WAT	W	13	19.973	21.293	36.711	1.00	38.84
ATOM	1664	OW0	WAT	W	14	14.757	-3.264	32.978	1.00	39.29
ATOM	1665	OW0	WAT	W	15	19.948	-2.552	48.084	1.00	39.94
ATOM	1666	OW0	WAT	W	16	13.394	-3.627	35.420	1.00	40.05
ATOM	1667	OW0	WAT	W	17	24.218	1.873	40.503	1.00	40.12
ATOM	1668	OW0	WAT	W	18	12.970	-9.846	41.166	1.00	40.24
ATOM	1669	OW0	WAT	W	19	29.332	23.835	36.728	1.00	40.10
ATOM	1670	OW0	WAT	W	20	32.982	14.615	37.196	1.00	40.03
ATOM	1671	OW0	WAT	W	21	15.963	-14.411	41.801	1.00	40.85
ATOM	1672	OW0	WAT	W	22	36.115	14.124	27.538	1.00	41.62
ATOM	1673	OW0	WAT	W	23	36.759	24.316	27.854	1.00	41.58
ATOM	1674	OW0	WAT	W	24	24.232	-12.120	40.700	1.00	41.18
ATOM	1675	OW0	WAT	W	25	20.170	8.808	43.184	1.00	41.55
ATOM	1676	OW0	WAT	W	26	14.174	8.391	52.525	1.00	43.14
ATOM	1677	OW0	WAT	W	27	25.412	3.713	30.549	1.00	41.48
ATOM	1678	OW0	WAT	W	28	14.723	-7.678	41.271	1.00	41.77
ATOM	1679	OW0	WAT	W	29	19.317	13.171	52.356	1.00	41.81
ATOM	1680	OW0	WAT	W	30	23.266	21.233	27.612	1.00	42.08
ATOM	1681	OW0	WAT	W	31	11.768	12.568	50.507	1.00	42.04
ATOM	1682	OW0	WAT	W	32	13.539	-13.131	41.639	1.00	42.18
ATOM	1683	OW0	WAT	W	33	11.508	10.524	52.379	1.00	42.93
ATOM	1684	OW0	WAT	W	34	3.363	-0.753	38.246	1.00	42.96
ATOM	1685	OW0	WAT	W	35	22.835	-3.224	40.382	1.00	43.01
ATOM	1686	OW0	WAT	W	36	26.824	22.825	28.526	1.00	43.00
ATOM	1687	OW0	WAT	W	37	18.644	-1.265	41.392	1.00	43.97
ATOM	1688	OW0	WAT	W	38	8.736	-6.966	49.493	1.00	43.69
ATOM	1689	OW0	WAT	W	39	15.651	-14.676	38.985	1.00	43.87
ATOM	1690	OW0	WAT	W	40	8.333	-12.297	37.586	1.00	44.06
ATOM	1691	OW0	WAT	W	41	25.939	7.843	39.161	1.00	44.11
ATOM	1692	OW0	WAT	W	42	10.384	9.683	30.485	1.00	44.27
ATOM	1693	OW0	WAT	W	43	0.943	8.083	43.152	1.00	44.34
ATOM	1694	OW0	WAT	W	44	21.071	2.692	43.998	1.00	44.65
ATOM	1695	OW0	WAT	W	45	16.203	7.540	48.658	1.00	44.83
ATOM	1696	OW0	WAT	W	46	21.491	-11.431	40.332	1.00	44.88
ATOM	1697	OW0	WAT	W	47	21.292	-1.593	41.871	1.00	45.24
ATOM	1698	OW0	WAT	W	48	33.051	8.145	30.148	1.00	45.89
ATOM	1699	OW0	WAT	W	49	11.644	15.303	50.268	1.00	46.78
ATOM	1700	OW0	WAT	W	50	35.864	19.699	14.264	1.00	46.41
ATOM	1701	OW0	WAT	W	51	7.067	6.695	50.824	1.00	46.58
ATOM	1702	OW0	WAT	W	52	27.033	16.432	44.207	1.00	47.45
ATOM	1703	OW0	WAT	W	53	12.107	-10.902	38.882	1.00	47.44
ATOM	1704	OW0	WAT	W	54	31.232	24.588	19.293	1.00	47.66
ATOM	1705	OW0	WAT	W	55	21.781	-3.130	44.031	1.00	47.48
ATOM	1706	OW0	WAT	W	56	7.169	-27.314	41.711	1.00	48.17
ATOM	1707	OW0	WAT	W	57	33.861	-1.778	23.374	1.00	48.53
ATOM	1708	OW0	WAT	W	58	33.357	8.082	26.362	1.00	48.51
ATOM	1709	OW0	WAT	W	59	26.396	24.163	13.998	1.00	49.70
ATOM	1710	OW0	WAT	W	60	21.233	20.044	43.429	1.00	49.73
ATOM	1711	OW0	WAT	W	61	39.604	24.739	18.318	1.00	49.28
ATOM	1712	OW0	WAT	W	62	24.974	-18.827	45.601	1.00	50.87
ATOM	1713	OW0	WAT	W	63	21.207	-0.654	31.876	1.00	49.81
ATOM	1714	OW0	WAT	W	64	13.203	8.179	28.792	1.00	50.30
ATOM	1715	OW0	WAT	W	65	21.887	5.385	43.977	1.00	50.58
ATOM	1716	OW0	WAT	W	66	24.468	6.206	27.276	1.00	50.23

ATOM	1717	OW0	WAT	W	67	16.159	-6.928	39.274	1.00	50.79
ATOM	1718	OW0	WAT	W	68	18.759	17.803	28.696	1.00	50.80
ATOM	1719	OW0	WAT	W	69	13.821	14.472	25.933	1.00	52.01
ATOM	1720	OW0	WAT	W	70	5.992	2.145	50.465	1.00	52.52
ATOM	1721	OW0	WAT	W	71	22.450	0.866	42.331	1.00	52.86
ATOM	1722	OW0	WAT	W	72	37.480	14.455	29.856	1.00	52.16
ATOM	1723	OW0	WAT	W	73	7.914	14.799	34.609	1.00	52.26
ATOM	1724	OW0	WAT	W	74	33.074	14.728	12.928	1.00	52.80
ATOM	1725	OW0	WAT	W	75	-2.139	5.177	35.817	1.00	53.07
ATOM	1726	OW0	WAT	W	76	8.849	6.339	29.567	1.00	53.08
ATOM	1727	OW0	WAT	W	77	2.499	9.596	40.507	1.00	53.22
ATOM	1728	OW0	WAT	W	78	8.453	-4.313	50.928	1.00	53.22
ATOM	1729	OW0	WAT	W	79	13.988	-16.279	37.477	1.00	54.52
ATOM	1730	OW0	WAT	W	80	29.311	23.613	25.169	1.00	53.94
ATOM	1731	OW0	WAT	W	81	10.698	17.607	37.556	1.00	53.87
ATOM	1732	OW0	WAT	W	82	10.533	-28.803	42.420	1.00	54.34
ATOM	1733	OW0	WAT	W	83	1.674	-0.659	35.990	1.00	54.11
ATOM	1734	OW0	WAT	W	84	13.238	5.649	29.129	1.00	54.35
ATOM	1735	OW0	WAT	W	85	23.172	23.184	42.047	1.00	53.98
ATOM	1736	OW0	WAT	W	86	25.591	-14.157	41.467	1.00	54.33
ATOM	1737	OW0	WAT	W	87	39.505	4.678	27.285	1.00	55.10
ATOM	1738	OW0	WAT	W	88	33.071	24.177	22.504	1.00	53.92
ATOM	1739	OW0	WAT	W	89	2.865	-14.306	47.361	1.00	55.09
ATOM	1740	OW0	WAT	W	90	10.824	5.199	27.990	1.00	54.87
ATOM	1741	OW0	WAT	W	91	13.268	-18.762	37.013	1.00	55.07
ATOM	1742	OW0	WAT	W	92	19.672	23.135	34.883	1.00	56.03
ATOM	1743	OW0	WAT	W	93	3.899	3.408	32.498	1.00	56.24
ATOM	1744	OW0	WAT	W	94	17.326	5.781	50.106	1.00	56.35
ATOM	1745	OW0	WAT	W	95	46.420	28.753	20.001	1.00	56.50
ATOM	1746	OW0	WAT	W	96	18.033	-25.950	38.021	1.00	56.78
ATOM	1747	OW0	WAT	W	97	16.668	11.173	20.729	1.00	57.28
ATOM	1748	OW0	WAT	W	98	-0.327	-1.130	37.865	1.00	56.31
ATOM	1749	OW0	WAT	W	99	13.791	-29.887	42.473	1.00	56.28
ATOM	1750	OW0	WAT	W	100	14.138	-6.120	36.256	1.00	56.78
ATOM	1751	OW0	WAT	W	101	-0.503	-1.004	43.200	1.00	56.68
ATOM	1752	OW0	WAT	W	102	7.034	2.268	29.920	1.00	57.78
ATOM	1753	OW0	WAT	W	103	39.612	16.983	21.840	1.00	57.56
ATOM	1754	OW0	WAT	W	104	12.322	-7.683	34.772	1.00	57.82
ATOM	1755	OW0	WAT	W	105	21.186	21.778	39.197	1.00	58.10
ATOM	1756	OW0	WAT	W	106	25.213	27.127	14.493	1.00	58.04
ATOM	1757	OW0	WAT	W	107	37.189	5.450	11.613	1.00	58.31
ATOM	1758	OW0	WAT	W	108	25.799	-17.600	47.916	1.00	58.58
ATOM	1759	OW0	WAT	W	109	25.505	0.503	36.518	1.00	57.70
ATOM	1760	OW0	WAT	W	110	21.154	19.292	24.315	1.00	58.80
ATOM	1761	OW0	WAT	W	111	23.932	23.123	29.269	1.00	58.45
ATOM	1762	OW0	WAT	W	112	30.025	16.034	12.701	1.00	58.92
ATOM	1763	OW0	WAT	W	113	5.440	-12.369	36.445	1.00	60.00
ATOM	1764	OW0	WAT	W	114	45.949	18.908	19.720	1.00	59.22
ATOM	1765	OW0	WAT	W	115	3.882	16.171	43.893	1.00	59.38
ATOM	1766	OW0	WAT	W	116	26.040	-17.629	41.513	1.00	58.92
ATOM	1767	OW0	WAT	W	117	13.942	-10.256	37.298	1.00	60.39
ATOM	1768	OW0	WAT	W	118	7.840	10.062	31.734	1.00	60.14
ATOM	1769	OW0	WAT	W	119	-1.860	-20.559	43.212	1.00	60.45
ATOM	1770	OW0	WAT	W	120	18.311	16.851	47.879	1.00	60.32
ATOM	1771	OW0	WAT	W	121	38.093	15.693	26.658	1.00	61.27
ATOM	1772	OW0	WAT	W	122	7.557	-26.418	44.769	1.00	61.39
ATOM	1773	OW0	WAT	W	123	17.200	-4.612	32.783	1.00	60.41
ATOM	1774	OW0	WAT	W	124	33.055	9.791	13.378	1.00	61.34
ATOM	1775	OW0	WAT	W	125	29.579	10.149	37.422	1.00	60.84
ATOM	1776	OW0	WAT	W	126	26.196	13.297	42.367	1.00	60.80
ATOM	1777	OW0	WAT	W	127	23.556	-4.737	42.642	1.00	61.18
ATOM	1778	OW0	WAT	W	128	10.687	-3.375	35.374	1.00	61.88
ATOM	1779	OW0	WAT	W	129	13.030	-13.947	38.339	1.00	62.52

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ATOM   1780  OW0 WAT W 130       9.747  -0.992  36.212  1.00 59.32
ATOM   1781  OW0 WAT W 131      24.814 -11.997  45.661  1.00 62.19
ATOM   1782  OW0 WAT W 132      23.200   4.574  23.546  1.00 61.90
ATOM   1783  OW0 WAT W 133      24.938  30.370  17.496  1.00 62.23
ATOM   1784  OW0 WAT W 134      35.459   1.260  16.603  1.00 62.66
ATOM   1785  OW0 WAT W 135      24.178  20.068  20.090  1.00 61.73
ATOM   1786  OW0 WAT W 136      40.127   0.350  18.771  1.00 62.44
ATOM   1787  OW0 WAT W 137      19.279  14.663  46.778  1.00 63.59
ATOM   1788  OW0 WAT W 138      20.090  20.354  46.023  1.00 62.81
ATOM   1789  OW0 WAT W 139      15.250  18.974  46.516  1.00 63.68
ATOM   1790  OW0 WAT W 140      21.267 -25.030  39.386  1.00 63.31
ATOM   1791  OW0 WAT W 141      26.107   2.756  33.033  1.00 63.89
ATOM   1792  OW0 WAT W 142      13.216  16.259  48.398  1.00 64.51
ATOM   1793  OW0 WAT W 143      23.474  19.596  51.112  1.00 65.45
ATOM   1794  OW0 WAT W 144       6.778  10.141  28.981  1.00 64.57
ATOM   1795  OW0 WAT W 145      23.613  15.848  49.685  1.00 64.50
ATOM   1796  OW0 WAT W 146      21.834  -6.518  36.556  1.00 65.24
ATOM   1797  OW0 WAT W 147      10.139 -10.444  36.806  1.00 65.85
ATOM   1798  OW0 WAT W 148      32.489  10.232  33.677  1.00 64.60
ATOM   1799  OW0 WAT W 149      31.655   6.263  27.510  1.00 64.29
ATOM   1800  OW0 WAT W 150       4.585 -20.934  39.031  1.00 66.94
ATOM   1801  OW0 WAT W 151      38.484  11.674  18.085  1.00 65.84
ATOM   1802  OW0 WAT W 152      42.438   8.992  21.219  1.00 65.71
ATOM   1803  OW0 WAT W 153      33.971  24.173  27.259  1.00 66.15
ATOM   1804  OW0 WAT W 154      24.597  -9.268  45.286  1.00 67.06
ATOM   1805  OW0 WAT W 155      -2.112 -26.008  50.039  1.00 66.08
ATOM   1806  OW0 WAT W 156       9.030 -32.481  39.896  1.00 66.14
ATOM   1807  OW0 WAT W 157      -3.216 -18.835  45.004  1.00 67.94
ATOM   1808  OW0 WAT W 158      -3.398   4.020  40.260  1.00 65.32
ATOM   1809  OW0 WAT W 159      25.878  24.231  20.622  1.00 68.10
ATOM   1810  OW0 WAT W 160      27.187   4.546  24.805  1.00 67.75
ATOM   1811  OW0 WAT W 161      24.071  24.303  35.784  1.00 67.51
ATOM   1812  OW0 WAT W 162       7.746  17.585  52.663  1.00 70.19
ATOM   1813  OW0 WAT W 163      19.301   4.980  47.873  1.00 68.23
ATOM   1814  OW0 WAT W 164      10.439  -4.135  32.539  1.00 65.45
ATOM   1815  OW0 WAT W 165      23.798  -0.930  41.113  1.00 68.64
ATOM   1816  OW0 WAT W 166       2.464   5.318  30.549  1.00 65.77
ATOM   1817  OW0 WAT W 167       9.665 -14.876  35.700  1.00 65.21
ATOM   1818  OW0 WAT W 168       1.759  10.431  44.227  1.00 69.25
ATOM   1819  OW0 WAT W 169      20.960   4.214  26.258  1.00 69.97
ATOM   1820  OW0 WAT W 170      28.769  24.807  27.878  1.00 67.86
ATOM   1821  OW0 WAT W 171      30.212  14.473   8.293  1.00 69.23
ATOM   1822  OW0 WAT W 172      20.178   0.312  50.589  1.00 70.29
ATOM   1823  OW0 WAT W 173      19.736   6.852  23.117  1.00 70.72
ATOM   1824  OW0 WAT W 174       8.978  16.807  50.514  1.00 70.10
ATOM   1825  OW0 WAT W 175      25.144  -1.759  34.429  1.00 71.96
ATOM   1826  OW0 WAT W 176      26.946  25.298  35.563  1.00 68.69
ATOM   1827  OW0 WAT W 177      44.918   5.619  13.054  1.00 70.16
ATOM   1828  OW0 WAT W 178      22.370  24.094  38.170  1.00 71.66
ATOM   1829  OW0 WAT W 179      -0.624  10.187  33.201  1.00 72.23
ATOM   1830  OW0 WAT W 180      11.015  17.856  47.520  1.00 71.42
ATOM   1831  OW0 WAT W 181       7.766   0.898  52.950  1.00 71.64
ATOM   1832  OW0 WAT W 182       3.469 -28.368  52.511  1.00 70.10
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Claims

1. A crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof, comprising residues vital for transcriptional and replicational activities of said protein.

2. An E2NT dimer protein according to Claim 1 wherein the residues lie on opposite sides of an N-terminal domain.

3. An E2NT dimer protein according to either preceding claim wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer.

4. An E2NT dimer according to Claim 3 comprising three clusters.

5. An E2NT dimer according to either of Claims 3 or 4 wherein a first cluster of vital residues is associated with interactions between N1 and N2 domains and comprises any one or more of the following residues Ile82, Glu90, Trp92, Lys112, Tyr138, Val145.

6. An E2NT dimer according to any one of Claims 3-5 wherein a second cluster of residues is associated with N1 interactions and comprises either or both of residues Trp33 and Leu94.

7. An E2NT dimer according to any one of Claims 3-6 wherein a third cluster of residues is associated with N2 interactions and comprises any one or more of the following residues Pro106, Lys111, Phe168, Trp134.

8. An E2NT dimer according to any preceding claim further comprising residues associated with transactivation and/or replication properties of E2.

9. An E2NT dimer according to Claim 8 wherein the residues comprise any one or more of the following residues Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69.

10. Use of a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein according to any preceding claim or homologue thereof in mapping mutations onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and the effect of mutations on folding of the E2 protein.

11. Use according to Claim 10 in rationalised antiviral drug design.

12. An *in vitro* method for identifying and/or selecting a candidate therapeutic agent, the method comprising determining interaction of a E2 N-terminal module (E2NT) dimer in a sample by contacting said sample with said candidate therapeutic agent and measuring DNA loop formation in E2.

13. Use of the method according to Claim 12 in identifying and/or selecting an antiviral candidate therapeutic agent.

14. Use according to Claim 13 wherein identification/selection of the candidate therapeutic agent depends on its ability to interfere with or block interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.

15. Use of an E2NT dimerisation inhibitor for the preparation of a medicament for treatment of conditions that arise as a result of HPV infection.

16. Use according to Claim 15 for the treatment of warts, proliferative skin lesions and/or cervical cancer.

17. A method of monitoring the efficacy of an antiviral therapy in a patient receiving a medicament for the treatment of an HPV infection comprising taking a sample from said patient and measuring E2NT interactions and/or DNA loop formation.

18. Use of a dimerisation surface of an crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof according to any one of Claims 1-9 as a target site for interaction with putative antiviral agents and/or for measuring efficacy of said agents.

19. A method for identifying and/or selecting a candidate therapeutic agent, comprising applying rationalised drug design to a crystal structure obtainable by crystallising E2NT, cryogenically freezing the crystals and generating the crystal structure using X-ray diffraction.

20. A method of claim 19, wherein the method by which the E2NT crystal structure is obtainable comprises crystallisation using hanging-drop vapour diffusion.

21. A method of claim 19 or claim 20 wherein the method by which E2NT crystal structure is obtainable comprises X-ray diffraction using uranium acetate and gold cyanide E2NT derivatives and refining with data extending to 1.9 Å spacing.

22. A method of any of claims 19 to 21, wherein the crystal structure comprises the portions of amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94.

23. A method of any of claims 19 to 22, wherein the rationalised drug design comprises designing drugs which interact with the dimerisation surface of E2NT.

24. A computer for producing a three-dimensional representation of a molecule or molecular complex, wherein said molecule or molecular complex comprises or a

three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3;

(b) a working memory for storing instructions for processing said machine-readable data;

(c) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

(d) a display coupled to said central-processing unit for displaying said three-dimensional representation.

25. The computer according to claim 24, wherein said three-dimensional representation is of a molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or wherein said three-dimensional representation is of a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

26. A computer for determining at least a portion of the structure coordinates corresponding to an X-ray diffraction pattern of a molecule or molecular complex, wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structural coordinates according to Table 3;

(b) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises an X-ray diffraction pattern of said molecule or molecular complex;

(c) a working memory for storing instructions for processing said machine-readable data of (a) and (b);

(d) a central-processing unit coupled to said working memory and to said machine-readable data storage medium of (a) and (b) for performing a Fourier transform of the machine readable data of (a) and for processing said machine readable data of (b) into structure coordinates; and

(e) a display coupled to said central-processing unit for displaying said structure coordinates of said molecule or molecular complex.

27. A crystallised molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

28. The crystallized molecule or molecular complex according to claim 27, wherein said molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or a homologue thereof, wherein said homologue has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

29. A machine-readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

30. The machine-readable data storage medium according to claim 7, wherein said molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

31. A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates according to Table 3; and said second set of data comprises an x-ray diffraction pattern of a molecule or molecular complex.

32. A method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex according to claim 27 or claim 28 comprising the steps of:

a. employing computational means to perform a fitting operation between the chemical entity and a dimerisation surface of the molecule or molecular complex; and

b. analysing the results of said fitting operation to quantify the association between the chemical entity and the dimerisation surface.

33. A drug or therapeutic agent identified, assessed or selected using a crystallised molecular complex of an E2NT protein or its crystal structure or using a complex of any of claims 1 to 9, a method of claim 12, a use of any of claims 13, claim 14 or 18. a method of any of claims 20 to24 or 32 or a product of any of claims 25 to 31.

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Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: TARGET FOR ANTIVIRAL THERAPY

(57) Abstract: A crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof, that comprises residues vital for viral transcription and/or replication. The invention also provides for the use of the dimer protein and interactions at its dimerisation surface in rationalised antiviral drug design.

FIG. 1. A

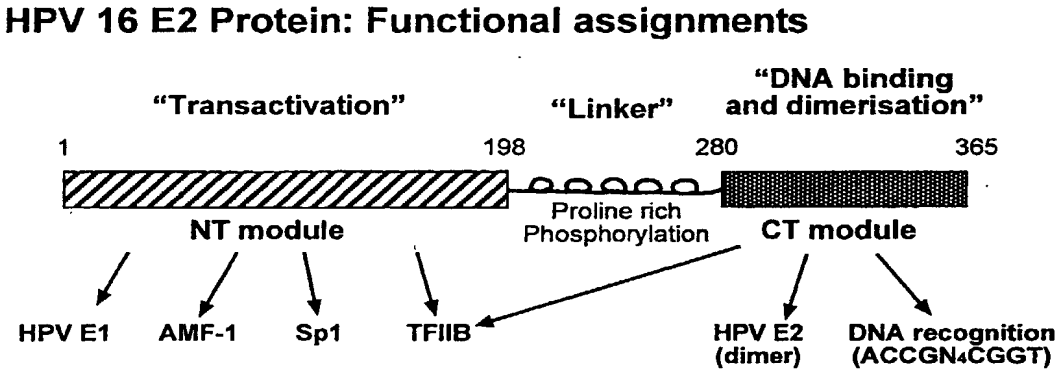

HPV 16 E2 Protein: Functional assignments
"Transactivation"
"Linker"
"DNA binding and dimerisation"
1
198
280
365
Proline rich Phosphorylation
NT module
CT module
HPV E1
AMF-1
Sp1
TFIIB
HPV E2 (dimer)
DNA recognition (ACCGN4CGGT)

Fig. 1.B

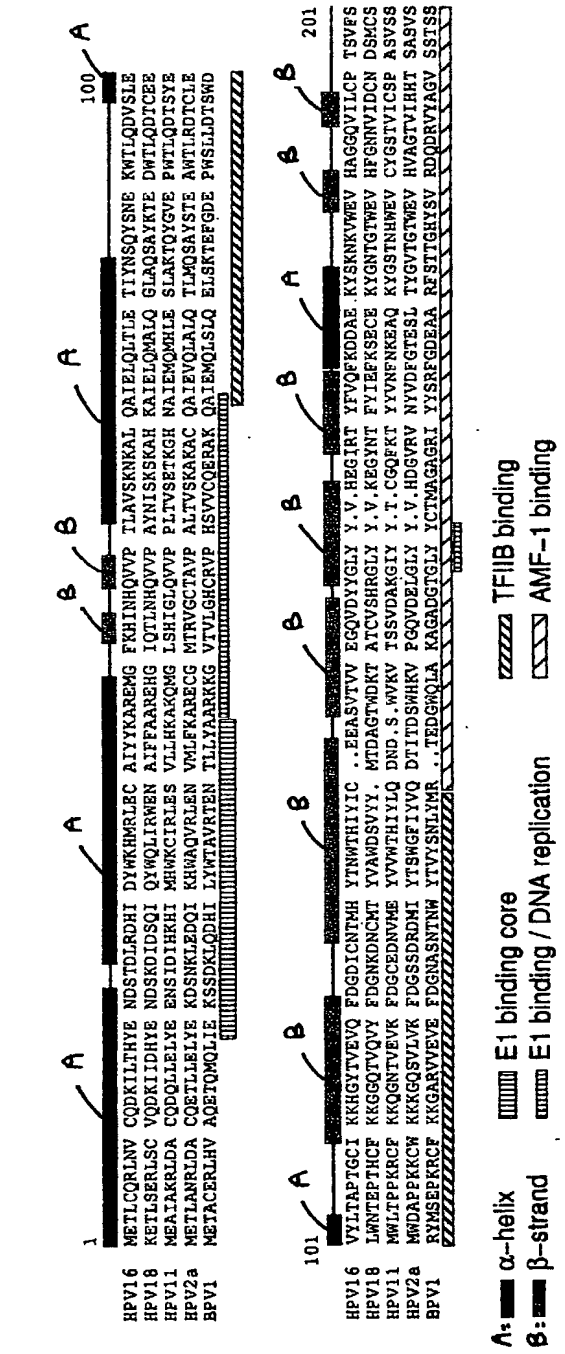
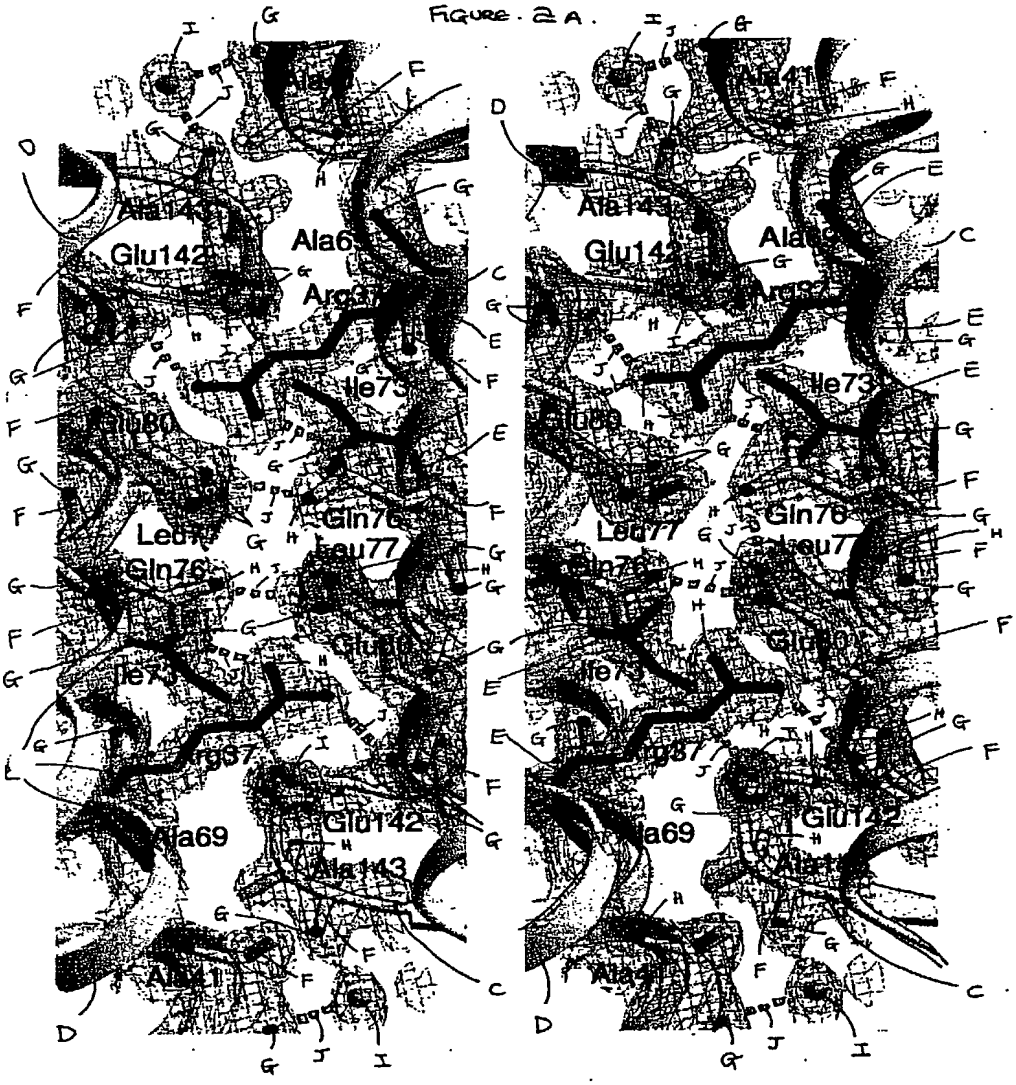
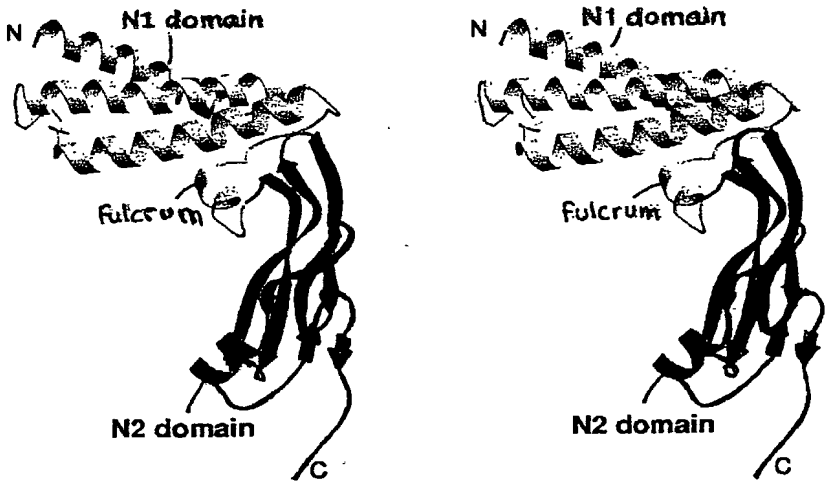

HPV16 METLCQRLNV CQDKILTHYE NDSTDLRDHI DYWKHMRLEC AIYYKAREMG FKHINHQVVP TLAVSKNKAL QAIELQLTLE TIYNSQYSNE KWTLQDVSLE
HPV18 KETLSERLSC VQDKIIDHYE NDSKDIDSQI QYWQLIRWEN AIFFAAREHG IQTLNHQVVP AYNISKSKAH KAIELQMALQ GLAQSAYKTE DWTLQDTCEE
HPV11 MEAIAKRLDA CQDQLLELYE ENSIDIHKHI MHWKCTRLES VLLHKAKQMG LSHIGLQVVP PLTVSETKGH NAIEMQMHLE SLARTQYGVE PWTLQDTSYE
HPV2a METLANRLDA CQETLLELYE KDSNKLEDQI KHWAQVRLEN VMLFKARECG MTRVGCTAVP ALTVSKAKAC QAIEVQLAIQ TLMQSAYSTE AWTLRDTCLE
BPV1 METACERLHV AQETQMQLIE KSSDKLQDHI LYWTAVRTEN TLLYAARKKG VTVLGHCRVP HSVVCQERAK QAIEMQLSLQ ELSKTEFGDE PWSLLDTSWD
HPV16 VTLTAPTGCI KKHGYTVEVQ FDGDICNTMH YTNWTHIYIC ..EEASVTVV EGQVDYYGLY Y.V.HEGIRT YFVQFKDDAE KYSKNKVWEV HAGGQVILCP TSVFS
HPV18 LWNTEPTHCF KKGGQTVQVY FDGNKDNCMT YVAWDSVYY. MTDAGTWDKT ATCVSHRGLY Y.V.KEGYNT FYIEFKSECE KYGNTGTWEV HFGNNVIDCN DSMCS
HPV11 MWLTPPKRCP KKQGNTVEVK FDGCEDNVME YVVWTHIYLQ DND.S.WVKV TSSVDAKGIY Y.T.CGQFKT YVVNFNKEAQ KYGSTNHWEV CYGSTVICSP ASVSS
HPV2a MWDAPPKKCW KKKGQSVLVK FDGSSDRDMI YTSWGFIYVQ DTITDSWHKV PGQVDELGLY Y.V.HDGVRV NYVDFGTESL TYGVTGTWEV HVAGTVIHHT SASVS
BPV1 RYMSEPKRCF KKGARVVEVE FDGNASNTNW YTVYSNLYMR ..TEDGWQLA KAGADGTGLY YCTMAGAGRI YYSRFGDEAA RFSTTGHYSV RDQDRVIAGV SSTSS
A: α-helix
B: β-strand
E1 binding core
E1 binding / DNA replication
TFIIB binding
AMF-1 binding

FIGURE 2A.



[C = blue; monomer ribbon : D = yellow; monomer ribbon : E = dark green; side chains of Arg37 and Ile 73 ; F = light green; side chains of other residues : G = O_2; red : H = blue; N_2 ; I = orange H_2O : J = dashed sticks ; hydrogen bonds]

FIGURE . 2B



N = N1 domain = aquamarine
m = fulcrum = green
L = N2 domain = pink

Fig. 2 C

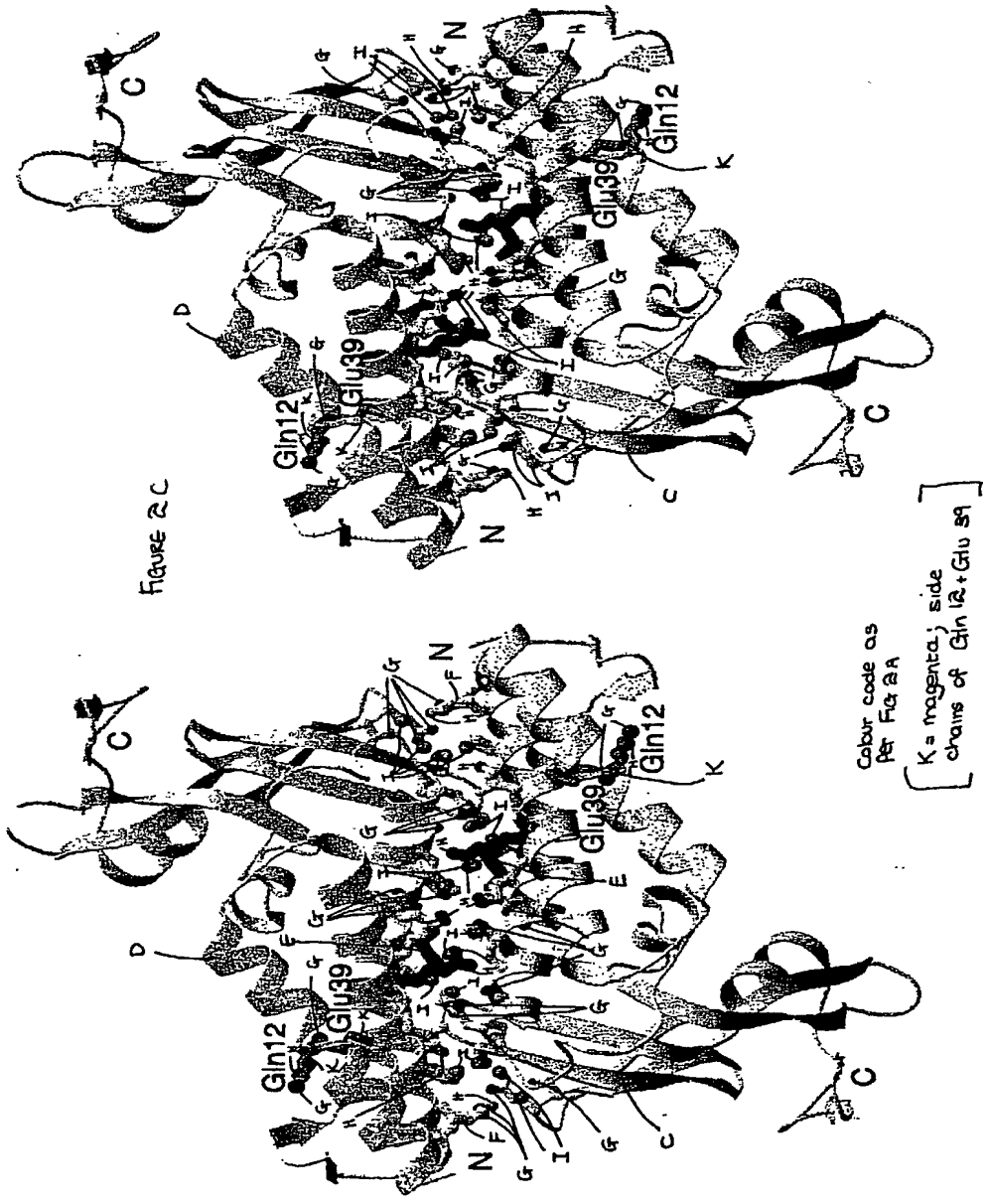


Figure 2C

Fig 3.A.

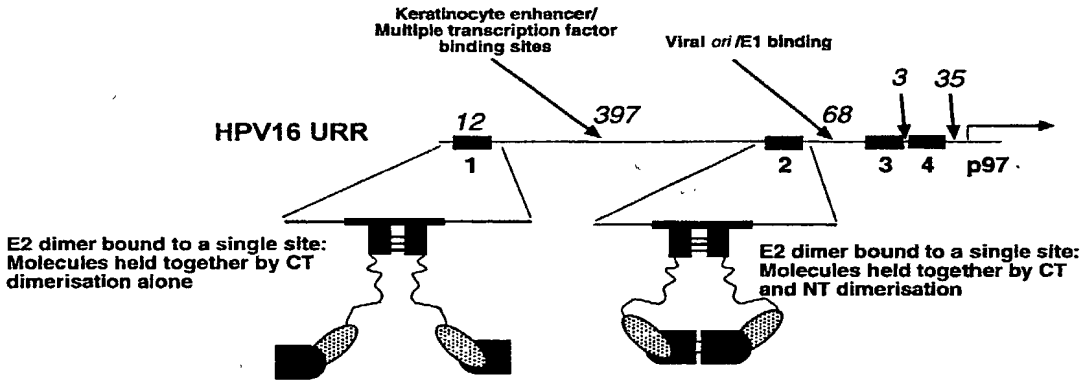

Keratinocyte enhancer/
Multiple transcription factor
binding sites
Viral ori /E1 binding
HPV16 URR
12
397
68
3
35
1
2
3
4
p97
E2 dimer bound to a single site:
Molecules held together by CT
dimerisation alone
E2 dimer bound to a single site:
Molecules held together by CT
and NT dimerisation

Fig. 3B

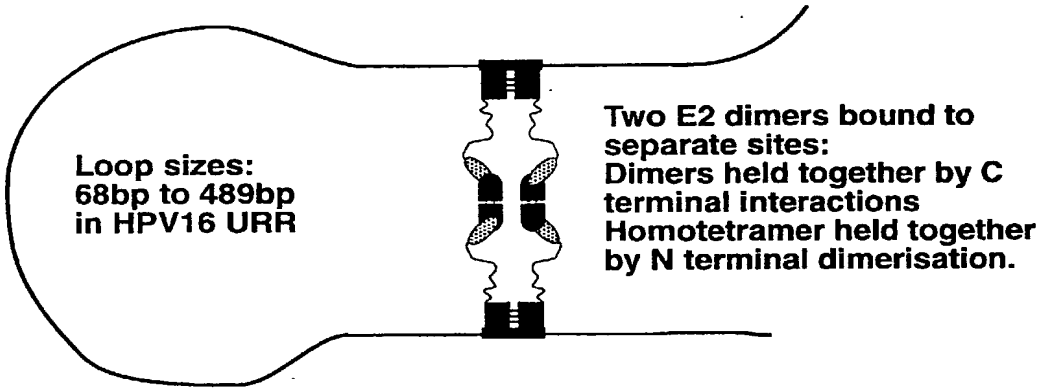

Loop sizes:
68bp to 489bp
in HPV16 URR
Two E2 dimers bound to separate sites:
Dimers held together by C terminal interactions
Homotetramer held together by N terminal dimerisation.

FIG. 3.C

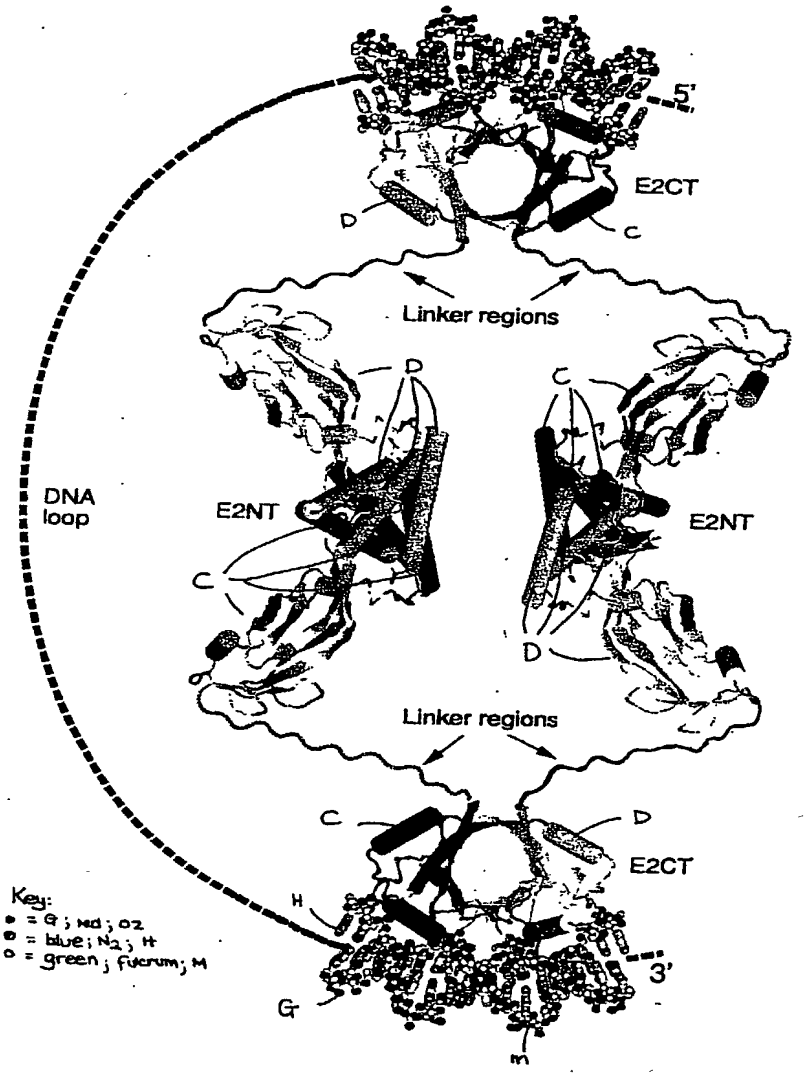

5'
E2CT
D
C
Linker regions
D
C
DNA
loop
E2NT
E2NT
C
D
Linker regions
C
D
E2CT
H
3'
G
M
Key:
● = O ; Md ; O2
● = blue ; N2 ; H
○ = green ; Fulcrum ; M

Fig. 3.D

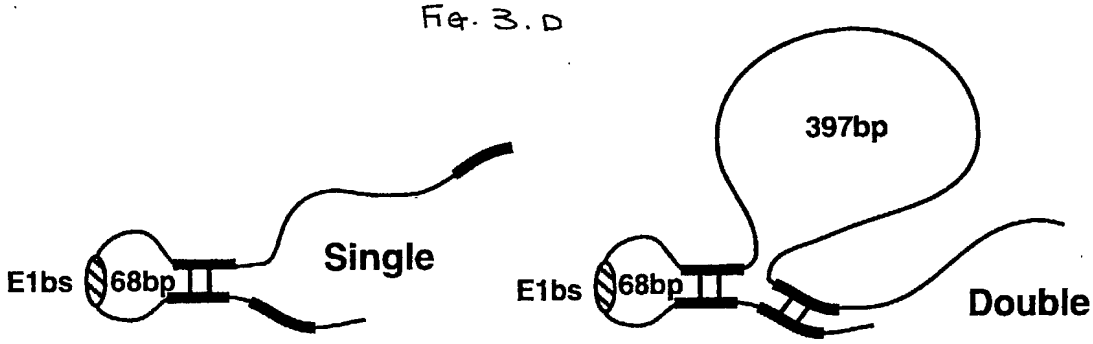
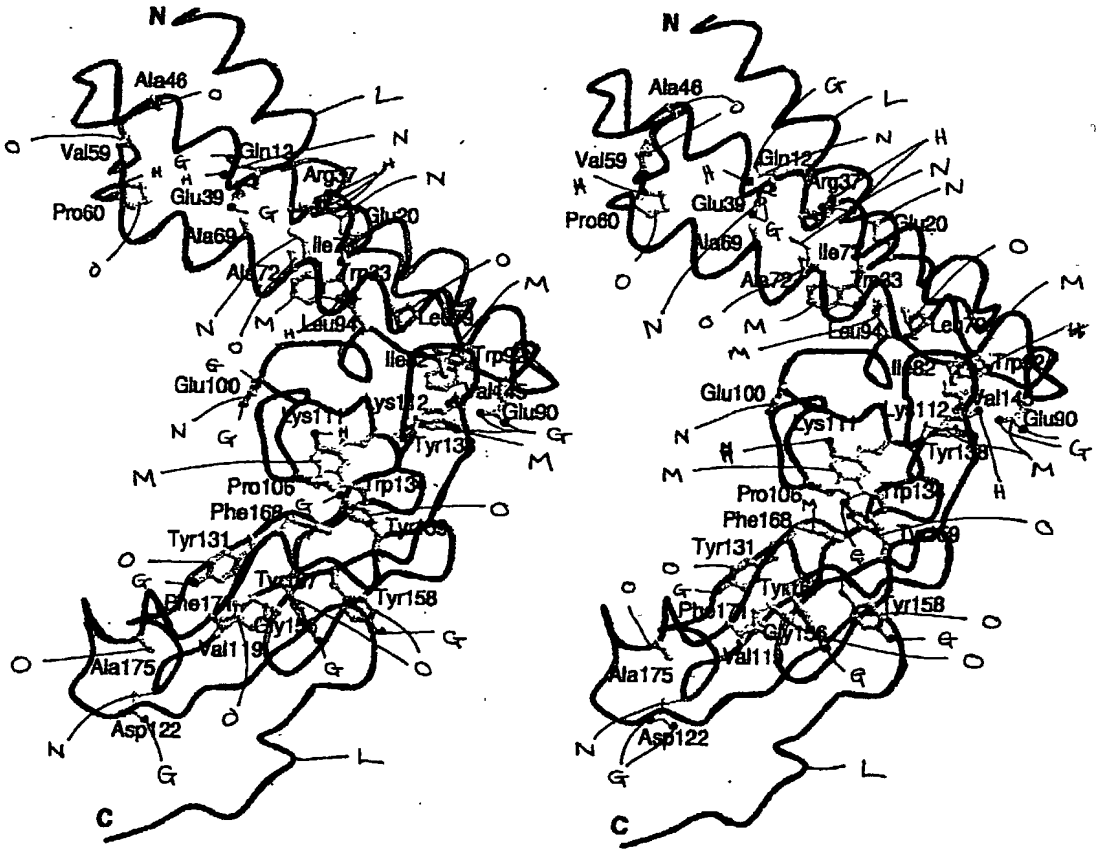


FIG. 4A.



O = yellow; sulphur atoms.

Fig. 4.B

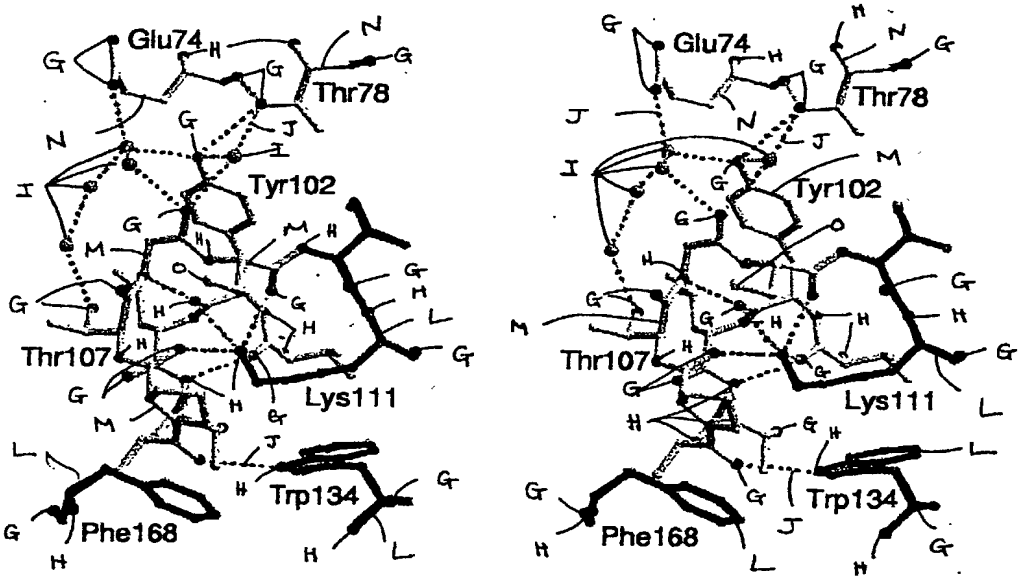

Glu74
Thr78
Tyr102
Thr107
Lys111
Trp134
Phe168
Glu74
Thr78
Tyr102
Thr107
Lys111
Trp134
Phe168

FIG. 4C

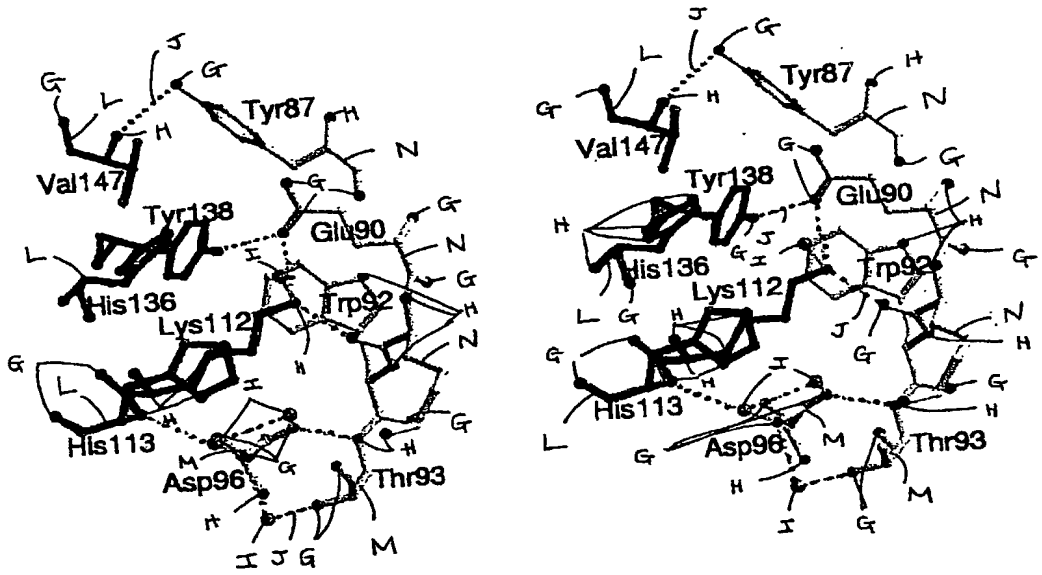
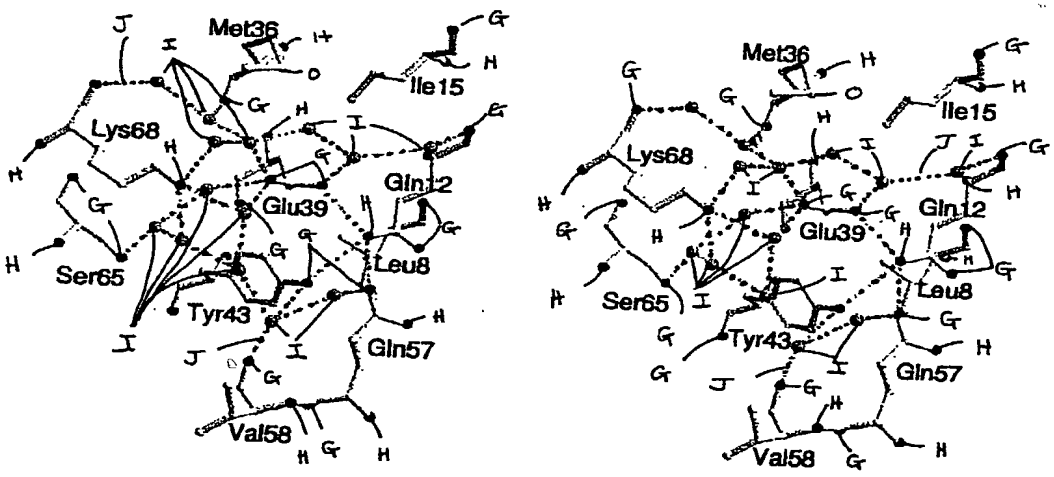

Val147
Tyr87
Tyr138
Glu90
His136
Lys112
Trp92
His113
Asp96
Thr93
Val147
Tyr87
Tyr138
Glu90
His136
Lys112
Trp92
His113
Asp96
Thr93

Figure 4D.


Met36
Ile15
Lys68
Gln12
Glu39
Leu8
Ser65
Tyr43
Gln57
Val58
Met36
Ile15
Lys68
Gln12
Glu39
Leu8
Ser65
Tyr43
Gln57
Val58

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

Attorney Docket No. 9052-111

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **TARGET FOR ANTIVIRAL THERAPY**,

the specification of which

☐ is attached hereto

OR

☒ was filed on **September 18, 2002** as United States Application No. or PCT International Application Number **PCT/GB00/03568** and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56, including material information that became available between the filing date of the prior application and the National or PCT International filing date of the continuation-in-part application, if applicable.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate, or of any PCT International application having a filing date before that of the application on which priority is claimed.

9921938.8	**Great Britain**	**09/17/1999**	☒ Yes ☐ No
Number	Country	MM/DD/YYYY Filed	Priority Claimed
			☐ Yes ☐ No
Number	Country	MM/DD/YYYY Filed	Priority Claimed
			☐ Yes ☐ No
Number	Country	MM/DD/YYYY Filed	Priority Claimed

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

None	
Application Number(s)	Filing Date (MM/DD/YYYY)
Application Number(s)	Filing Date (MM/DD/YYYY)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or § 365(c) of any PCT international application designating the United States of America, listed below.

PCT/GB00/03568	09/18/00	Published
Appln. Serial No.	Filing Date	Status Patented/Pending/Abandoned
Appln. Serial No.	Filing Date	Status Patented/Pending/Abandoned
Appln. Serial No.	Filing Date	Status Patented/Pending/Abandoned

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following registered attorney(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. I also appoint the following registered attorney(s) to represent me before all competent International Authorities in connection with any and all international applications filed by me with an appropriate receiving office claiming priority to the U.S.

application. I also appoint the following registered attorney(s) to make or receive payment on my behalf in connection with the filing of such international applications.

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